Management of the Primary Tumor in Metastatic Colorectal Cancer

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By

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ABSTRACT

Background

Systemic therapy is the mainstay of treatment for stage IV colorectal cancer (CRC) and provides meaningful survival benefit. Currently, there is very low quality evidence available regarding benefit of primary tumor resection in patients with metastatic CRC. In spite of uncertain survival benefit, high rates of surgical resection have been reported in patients with unresectable metastatic disease. There is a lack of randomized clinical trial to address this important question in patients with stage IV CRC. Although several observational studies have suggested potential survival benefit of primary tumor resection, lack of randomization and failure to control important prognostic variables such as performance status, are major critiques to the findings of the observational studies. We have undertaken this large population-based cohort study to determine the survival benefit of primary tumor resection in stage IV CRC by minimizing various biases reported in the literature.

Hypothesis

We hypothesized that primary tumor resection in patients with stage IV CRC improves survival independent of chemotherapy and other known prognostic variables.

Objectives

- To systematically review the published literature and synthesize the data in relation to primary tumor resection in stage IV CRC.
- To compare survival of patients with stage IV CRC who underwent primary tumor resection with the patients who did not have surgery and to determine the prognostic importance of surgery of the primary tumor in stage IV CRC.
- To determine survival advantage of primary tumor resection in patients with stage IV CRC and minimally symptomatic or asymptomatic primary tumor.
- To determine survival advantage of primary tumor resection in patients with stage IV CRC during the period of modern chemotherapy.

Methods

The study was conducted in two phases. During the first phase, a systematic review of published literature was performed using the Medline, EMBASE and CENTRAL databases. Studies were selected by using pre-specified eligibility criteria with restriction to publication dates from 1980 onward, English language, and human studies. Articles that met the inclusion criteria were assessed for quality by using the Ottawa-Newcastle score & GRADE. Data was collected and synthesized as per the PRISMA guideline. In the second phase, population-based retrospective cohort studies were performed. The study population was comprised of patients with stage IV CRC diagnosed during the period of January 1992 to December 2010 in the province of Saskatchewan, Canada. The prognostic significance of primary tumor resection was initially evaluated in patients' cohort with stage IV CRC diagnosed during 1992-2005 period. The results were validated in a

second patients cohort diagnosed during 2006-2010. Survival was calculated using the Kaplan-Meier method. Survival distributions of different groups were compared by the log-rank tests. Cox proportional multivariate regression analyses were performed to determine survival benefit of primary tumor resection by controlling the other prognostic variables.

Results

Systematic review: Of total of 3379 reports, 15 retrospective observational studies were selected. Of total 12456 patients, 8620 (69%) underwent primary tumor resection. Median overall survival of the resection group was 15.2 months (range: 10-30.7) compared with 11.4 months (range: 3-22) in the non-resection group. Hazard ratio (HR) for survival was 0.69 (95% CI: 0.61-0.79), which favors surgical resection. Mean postoperative mortality and nonfatal complications rates were 4.9% (95% CI: 0-9.7) and 25.9% (95% CI: 20.1-31.6), respectively.

Cohort Studies: A total 1378 eligible patients were identified during the period of 1992-2005. Nine hundred and forty-four (68.5%) underwent primary tumor resection. Among 1378 patients, 42.3% received chemotherapy. Cox proportional analyses revealed that use of chemotherapy (HR 0.47, 95% CI: 0.41-0.54), primary tumor resection (HR 0.49, 95% CI: 0.41-0.58), second-line chemotherapy (0.47, 95% CI: 0.45-0.64), and metastasectomy (HR 0.54, 95% CI: 0.45-0.64) were correlated with superior survival. In a subcohort of 834 patients with asymptomatic or minimally symptomatic disease, primary tumor resection was correlated with better survival (HR 0.47; 0.39-0.57). Test for interaction between $\geq$1 metastatic sites and surgery was significant suggesting a larger benefit of surgery in patients with stage IVa disease.

These findings were validated in a cohort of 569 patients with stage IV CRC diagnosed during the period of 2006-2010. Fifty seven percent patients received chemotherapy and 91.4% received modern chemotherapy. Median overall survival of patients who received all active agents and underwent primary tumor resection was 39 months (95% CI: 25.1-52.9). In multivariate analysis, primary tumor resection, hazard ratio (HR):0.44 (95% CI: 0.35-0.56), was correlated with superior survival.

Conclusions

Our study supports primary tumor resection in patients with stage IV CRC. It correlates with better survival independent of known prognostic variables such as chemotherapy, metastasectomy, performance status and comorbid illness. In a subgroup of asymptomatic or minimally symptomatic patients or who were treated with modern chemotherapy and biologics, primary tumor resection was correlated with better survival.

Summaries of Companion Studies

1. Predictive factors of use of systemic therapy in stage IV colorectal cancer

Although in a clinical trial setting, strict eligibility criteria are used for chemotherapy, little is known about the use of chemotherapy in the general population. The study aims to assess clinicopathological variables that correlate with the use of chemotherapy in patients with stage IV CRC. A total of 1,237 eligible patients were identified. A multivariate logistic regression analysis revealed that age <65 year (odd ratio [OR] 3.82, 95% CI:2.59-5.63), metastasectomy (OR 3.60, 95% CI:1.82-7.10), normal albumin (OR 3.26, 95%CI:2.44-4.36), absence of comorbid illness (OR 2.87, 95% CI:1.34-6.16), ECOG performance status of <2 (OR 2.72, 95% CI:1.94-3.82), normal blood urea nitrogen (OR 2.24, 95% CI:1.40-3.59), palliative radiation (OR 2.03, 95% CI:1.38-2.99), primary tumor resection (OR 2.00, 95% CI:1.47-2.73), and the time period (OR 1.85, 95% CI:1.41-2.42) were significantly correlated with the use of chemotherapy.

2. Regional Lymph Nodes Status in Stage IV Colorectal Cancer

Lymph nodes status and the ratio of metastatic to examined lymph node (LNR) are important prognostic factor in early-stage colorectal cancer (CRC); however, their significance in patients who have already developed distant metastases remains unknown. The study aims to determine prognostic importance of nodal status and the LNR in patients with stage IV CRC who underwent primary tumor resection. Among 1109 eligible patients who underwent primary tumor resection, no chemotherapy, HR: 2.36 (95% CI:2.0-2.79); not having metastasectomy, HR: 1.94 (95% CI:1.63-2.32); ratio of metastatic to examined lymph node ≥0.36, HR: 1.59 (95% CI:1.38-1.84); nodal status, HR 1.34 (95% CI:1.14-1.59); and T status, 1.23 (95% CI:1.07-1.40) were correlated with survival.

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DEDICATION

This work is dedicated to my late parents Fatima and Yaqub for their endless love, affection, encouragement, and prays and to the people with cancer and their families for their strength, courage and contributing new knowledge.

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ABBREVIATIONS

AIDS - Acquired Immune Deficiency Syndrome
AIO - The Arbeitsgemeinschaft Internistische Onkologie
AJCC - American Joint Committee on Cancer
ALP - Alkaline phosphatase
ASCO - American Society of Clinical Oncology
BRAF - Murine sarcoma viral oncogene homolog B
BUN - urea nitrogen
CAIRO - the Capecitabine, Irinotecan, and Oxaliplatin in advanced colorectal cancer
CEA - carcinoembryonic antigen
CENTRAL - The Cochrane Central Register of Controlled Trials
CHIR-Net - the German Surgical Network of Clinical Studies
CPC - the Canada Post Corporation
CRC - colorectal cancer
ECOG - Eastern Cooperative Oncology Group
EGFR - epidermal growth factor receptor
ELISA - enzyme-linked immunosorbent assay
ESMO - European Society of Medical Oncology
EMBASE - Excerpta Medica dataBASE
5-FU - -5-fluorouracil
FOLFOX - 5FU, leucovorin and oxaliplatin
FOLFIRI - 5FU, leucovorin and irinotecan
FOLFOXIRI - FU, leucovorin, oxaliplatin and irinotecan
GIST - gastrointestinal stromal tumor
HR - Hazard Ratio
ICD - International Classification of Disease
95% CI - 95 percent confidence interval
KPM - Kaplan-Meier method
KRAS - Kirsten rat sarcoma viral oncogene homolog
LNR - the ratio of metastatic to examined lymph node
M: F - male: female
NOS - Newcastle-Ottawa Quality Assessment Scale
NSABP - The National Surgical Adjuvant Breast and Bowel Project
NCCN - National Comprehensive Cancer Network
MEDLINE - Medical Literature Analysis and Retrieval System Online
OR - Odd ratio
OS - over survival
PCCF - the Postal Code Conversion File
PH - proportional hazards
PICO - population, intervention, comparison, outcome
PS- performance status
QOL - Quality of life
RCT - randomized controlled trials
SAFEI2 - socio-economic Factor Index 2
SDGC - the Study Centre of the German Surgical Society

SEER - the Surveillance, Epidemiology, and End Results
SES - socioeconomic status
SRPT - surgical resection of the primary tumor
STROBE - The Reporting of Observational Studies in Epidemiology
VEFF - vascular endothelial growth factor
WBC - white blood cell

CHAPTER 1 - INTRODUCTION

1.1 Background

1.1.1 Epidemiology of Colorectal Cancer

Colorectal Cancer (CRC) is a major cause of morbidity and mortality (1-4). Every year at least 600,000 people die of this kind of cancer. It is the third most common cancer and the fourth most common cause of cancer death worldwide. In 2012 approximately 1.4 million people were diagnosed with CRC, which accounts for over 9% of global cancer incidence (1). The incidence of CRC varies about 15-fold across various geographic regions in the world. Approximately one in 20 people in developed countries will develop CRC in their life time; the case fatality from this disease is 33%. In North America, CRC is the third most common cancer diagnosis among men and women and is the second leading cause of cancer-related death (2-5).

Each year more than 20,000 Canadians are diagnosed with CRC, and approximately 9,000 die from the cancer (5). One in 14 men and one in 15 women will develop CRC during their lifetime. In 2015, this translated into 14,000 new cases in men and 11,100 new cases in women in Canada. The case fatality for men is one in 27 and for women one in 31. CRC is the second leading type of cancer incidence in men (14%) and the third one in women (12%). (5)

Advances in screening and diagnostic methods have contributed to early detection and better staging. Despite the advent of CRC screening program approximately 20 to 25% of patients with CRC are diagnosed with synchronous metastatic CRC (4). Whereas surgery is the primary treatment for early stage CRC and chemotherapy with or without radiation is used in high risk disease to reduce the risk of recurrence (3-5), systemic therapy is the mainstay of treatment for Stage IV CRC (6-9) [**Figure 1.1**].

1.1.2 Treatment of Stage IV Colorectal Cancer

There are several known and unknown factors that may affect survival of patients with newly diagnosed CRC (**Figure 1.2**). Although for the majority of patients with stage IV CRC there are no curative options, a significant improvement in survival can be achieved with systemic treatment. The median overall survival (OS) of patients with stage IV CRC with best supportive care alone is only about 6 months (10). Systemic therapy, comprising chemotherapy and targeted therapy, provides meaningful improvements in median survival and progression-free survival (11-29). The last fifteen years have seen remarkable improvements in the survival of patients with stage IV CRC, which is primarily attributed to the availability of several novel agents, metastasectomy and other liver-directed therapies in selected patients. For many years, 5-fluorouracil (5-FU) was

the only active agent available in the management of patients with stage IV CRC (11, 12). Access to several novel agents has significantly improved the survival of patients with Stage IV CRC. These agents include two cytotoxic agents (irinotecan and oxaliplatin) and three humanized monoclonal antibodies (e.g., bevacizumab and cetuximab and panitumumab) that target vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR). More recently regorafenib, an orally active inhibitor of angiogenic/stromal/oncogenic receptor tyrosine kinases, and aflibercept a recombinant fusion protein that interferes with VEGF binding, have also improved survival in this particular patient population (13-28).

Overall, with the judicious use of active agents in the management of CRC, the median OS of patients with advanced CRC has increased to about 30 months (29) [**Figure 1.3**]. Survival is improved when patients are exposed to all available cytotoxic drugs during the course of their disease (30). The five-year OS for patients who are diagnosed with distant metastases ranges from 5-20 %.(31-33). However, only a small percentage of patients with advanced CRC achieve long-term remission.

1.1.3 Surgical Management of Stage IV CRC

The role of surgery in stage IV CRC has evolved over the past decade. For example, surgery is performed with a curative intention by removing the metastatic lesions and primary tumor or it is contemplated for the palliation of symptoms via removal of the primary tumor (4, 6, 8, 34-38). Among patients presenting with synchronous distant metastases, approximately 15 - 20% have metastases that are resectable for cure. Complete resection of the primary tumor with metastatic lesions in these patients has been associated with durable remission in approximately 30-40% cases (34-39). Nevertheless, only a subset of patients with limited liver and or lung metastases can be cured with multimodality therapy. The optimal surgical management of Stage IV CRC that is not amenable to curative resection is unknown. Although administration of systemic therapy in patients with metastatic CRC may convert unresectable into resectable disease, for most patients the principal goal of treatment is to prolong survival and only about 10-15% patients are alive at 5 years. Primary tumor resection in patients with incurable metastatic disease is usually recommended for palliative purposes to manage obstruction, perforation, or bleeding. In spite of the uncertain survival benefit, a high rate of surgical resection has been reported in patients with unresectable metastatic disease.

For instance, two population-based studies that were designed to examine patterns of surgical practice in patients with advanced CRC reported primary tumor resection rates of 66-72% (40, 41). Both studies utilized data obtained during the period of monotherapy with 5-FU and the current rate of resection of primary tumor with the introduction of new generation treatment is not known. Nevertheless, a recent retrospective cohort study using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results CRC registry suggested a trend toward fewer primary tumor resections during the period of modern chemotherapy (42). Of 64,157 patients, diagnosed with stage IV CRC, 67.4% had undergone primary tumor resection. The annual rate of primary tumor resection decreased significantly from 74.5% in 1988 to 57.4% in 2010.

1.2 Rationale for the Study

The benefit of primary tumor resection in patients with synchronous unresectable metastases is not known. Even though enormous progress has been made in the treatment of patients with CRC within the past three decades, the optimal management of patients with metastatic disease not amenable to curative therapy, who present without severe primary tumor- related symptoms, is remained controversial. Primary tumor resection in patients with stage IV cancer is often performed to deal with presenting primary tumor symptoms and/or to prevent future primary tumor complications. Palliative primary tumor resection in patients with advanced solid cancers may prevent local tumor complications and improve disease control by reducing the tumor bulk. In advanced ovarian and renal cell cancer, surgical resection of the primary tumor has shown significant survival benefit (43, 44). The primary tumor may secrete cytokines that promote tumor growth and reduce response to cytotoxic agents (45).

1.2.1 Arguments for Surgery

Potential advantages of primary tumor resection in stage IV CRC are prevention of obstruction and major bleeding, better pain control, and potential reduction in serious adverse effects related to novel targeted therapy such as bleeding and perforation. The primary tumor complication rates including obstruction, perforation, and hemorrhage have been reported to be as high as 63% (40). Stillwell and others have demonstrated that patients who were treated with upfront chemotherapy were 7.3 times more likely to have a complication from the primary tumor. Furthermore, when these patients were operated for the primary tumor-related complications, they were more likely to have a poor postoperative outcome (46). Hence, surgical resection of primary tumor may facilitate treatment tolerance with better response and potentially improve survival.

Removal of the primary tumor results in reduction in the disease burden. This may result in alteration in the host immune response and a better outcome.

1.2.2 Arguments Against Surgery

Conversely, the newer generation chemotherapy in combination with targeted therapy has been associated with response rate of 40-60% (29, 47). Complications following primary tumor resection in patients with advanced CRC can delay or prevent initiation of systemic therapy and thereby precludes benefit associated with it. There is no evidence that primary tumor response rates are inferior to those of metastases. Systemic therapy not only reduces the size of metastatic lesions but also shrinks the primary tumor, thereby potentially decreases local complications related to an intact primary tumor such as bowel obstruction (48, 49). For example, Karoui and others have demonstrated that 70% of patients with stage IV CRC had major histological responses in the primary tumor following preoperative chemotherapy, which suggests that treatment with chemotherapy can be effective in the majority of patients (50). Three retrospective studies specifically investigated the risk of primary tumor complication in patients with non-resection management (51-54). Muratore and others demonstrated that only one out of 35 patients who were treated with oxaliplatin-based chemotherapy developed major complications related to the primary tumor (51). Sarlea and others reported an obstruction rate of 17% with the use of single agent 5FU.

In their study 12% patients required surgery for worsening pain (52). In the study by Clement and others, 3 of 37 patients developed obstruction during palliative chemotherapy and were managed with defunctioning stoma and stent (53).

There remains a risk of perforation when combining anti-VEGF therapy with cytotoxic agents in patients with intact primary tumors (54). A retrospective study evaluated the frequency of interventions necessary to palliate the intact primary tumor in patients with synchronous, stage IV CRC who received up-front modern combination chemotherapy. Of 233 patients, 7% required emergent surgery for primary tumor obstruction or perforation, 4% required non-operative interventions (i.e. stent or radiotherapy), and 89% never required any direct symptomatic management for their intact primary tumor. The authors concluded that most patients with synchronous, advanced CRC who receive up-front systemic therapy never require palliative surgery for their primary tumors, and that systemic therapy can be administered safely to these patients. Nevertheless, the median overall survival of these patients was only 13 months, while median overall survival of 20-24 months has consistently been reported for patients with stage IV CRC in phase III trials (55). The National Surgical Adjuvant Breast and Bowel Project subsequently conducted a phase II trial (NSABP C-10) using FOLFOX (5-FU, leucovorin and oxaliplatin) and bevacizumab combination in 85 patients with synchronous Stage IV CRC. Overall 14% patients developed major complications including obstruction, perforation, bleeding, or death related to an intact primary tumor. Median overall survival for the treated cohort was 19.9 months. The author concluded that combining bevacizumab with chemotherapy did not result in unacceptable complication rates related to an intact primary tumor and that these patients can be spared initial non-curative resection of the primary colon tumor (56).

While the benefit of metastasectomy is well established in the setting of oligometastases, surgical removal of the primary tumor in patients with unresectable metastases remains controversial. There is still considerable uncertainty as to whether patients with advanced CRC with few or no symptoms related to the primary tumor should undergo surgery prior to systemic therapy and whether elective surgery in patients with advanced colorectal cancer will have a survival advantage independent of the use of systemic therapy. Currently, there is very low quality evidence available regarding survival benefit of primary tumor resection, in patients with Stage IV CRC and otherwise unresectable metastatic lesions. No randomized trials are available to guide the management of the primary tumor in patients with unresectable metastatic CRC. Most are single institutional small retrospective studies conducted during the period of mono therapy with a fluoropyrimidine compound. While some have advocated for surgery (57-66), other have failed to demonstrate survival benefit with the resection of primary tumor in patients with advanced CRC (67-71). Furthermore, it is not known if a similar benefit can be achieved during the period of second- and third-generation anti-cancer agents which are associated with a higher response rate and a better overall survival in patients with advanced CRC.

We propose a large population-based cohort study to analyze the role of primary tumor resection in metastatic colon cancer. In the absence of randomized controlled trials and well-designed large population-based studies, this study is undertaken, to investigate the optimal surgical management of patients diagnosed with synchronous stage IV CRC cancer by controlling for various known confounding factors including age, comorbid illness, performance status and other important

prognostic variables. Furthermore, this study also investigates prognostic significance of various patients- and tumor-related factors and other interventions in stage IV CRC.

Chemotherapy is known to be one of the most important prognostic variables in patients with stage IV CRC. In a companion study we evaluated prevalence of use of chemotherapy in patients with stage IV CRC and its correlation with several clinicopathological factors.

Given the fact that little is known about the prognostic significance of nodal involvement in stage IV CRC, in a second companion study, we examined the relationship between regional nodal status and other tumor-related factors and survival in patients with stage IV CRC.

1.3 Hypothesis

We hypothesize that surgical resection of the primary tumor, in patients with synchronous stage IV colorectal cancer, improves survival independent of the use of systemic therapy and other known prognostic variables.

1.4 Objectives

- To systematically review the published literature and synthesize the data in relation to primary tumor resection in stage IV CRC.
- To compare survival of patients with stage IV CRC who underwent primary tumor resection with the patients who did not have surgery and to determine the prognostic importance of surgery of the primary tumor in stage IV CRC.
- To determine survival advantage of primary tumor resection in patients with stage IV CRC and minimally symptomatic or asymptomatic primary tumor.
- To determine survival advantage of primary tumor resection in patients with stage IV CRC during the period of modern chemotherapy.

1.5 Objectives of Companion Studies

- To examine various patients and tumor-related characteristics and co-interventions that are associated with the use of chemotherapy in patients with stage IV CRC.
- To determine the prognostic significance of primary tumor-related factors in patients who underwent surgical resection of the primary tumor.

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Figure 1.1: A management framework for CRC. Patients with early stages CRC (stage I-III) are treated with surgery with or without chemotherapy and radiation. Patients with stage IV CRC are primarily treated with chemotherapy. A selected group of patients can be cured with metastasectomy.

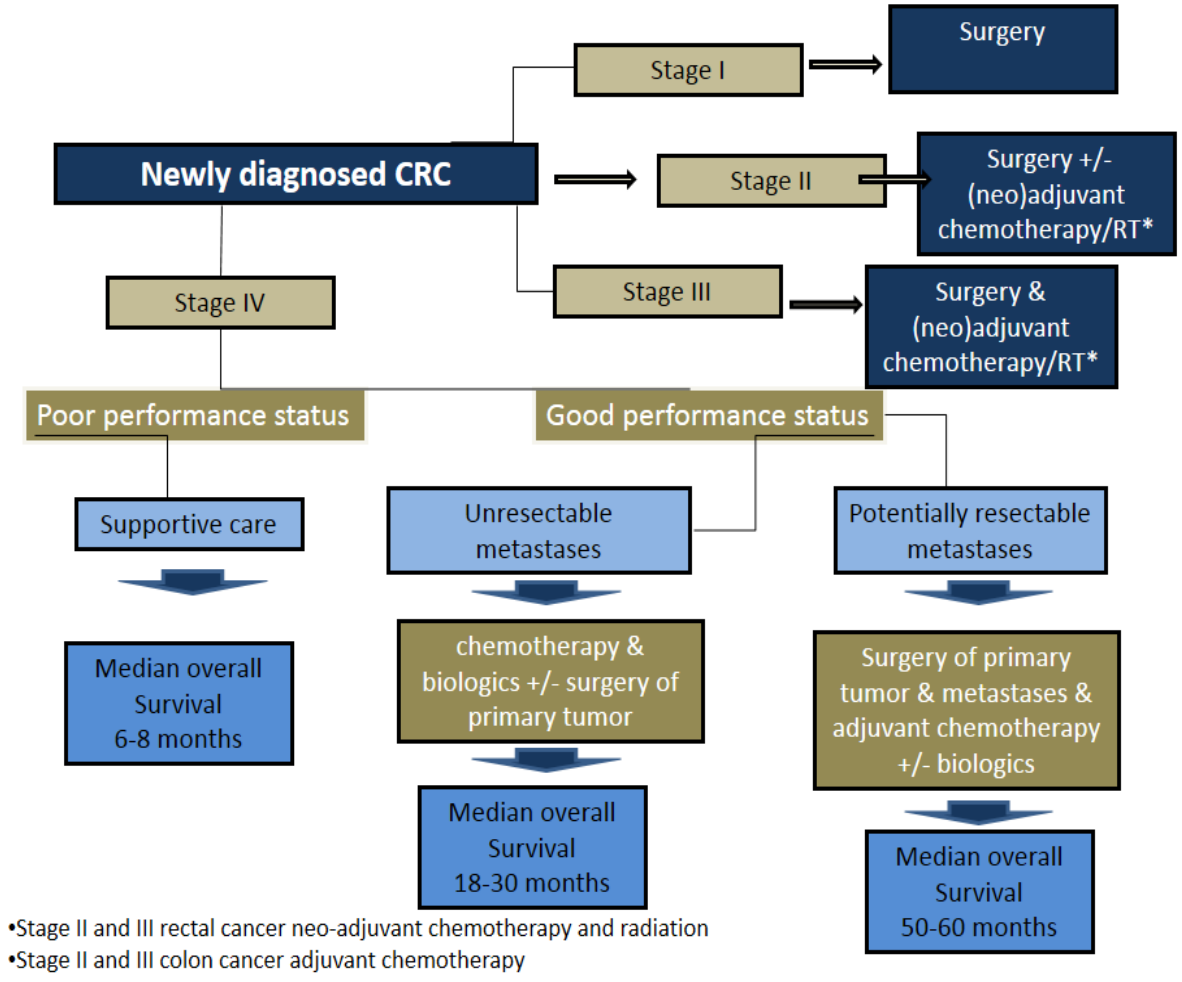


Figure 1.2: Potential factors that may correlate with outcome of patients with newly diagnosed metastatic colorectal cancer.

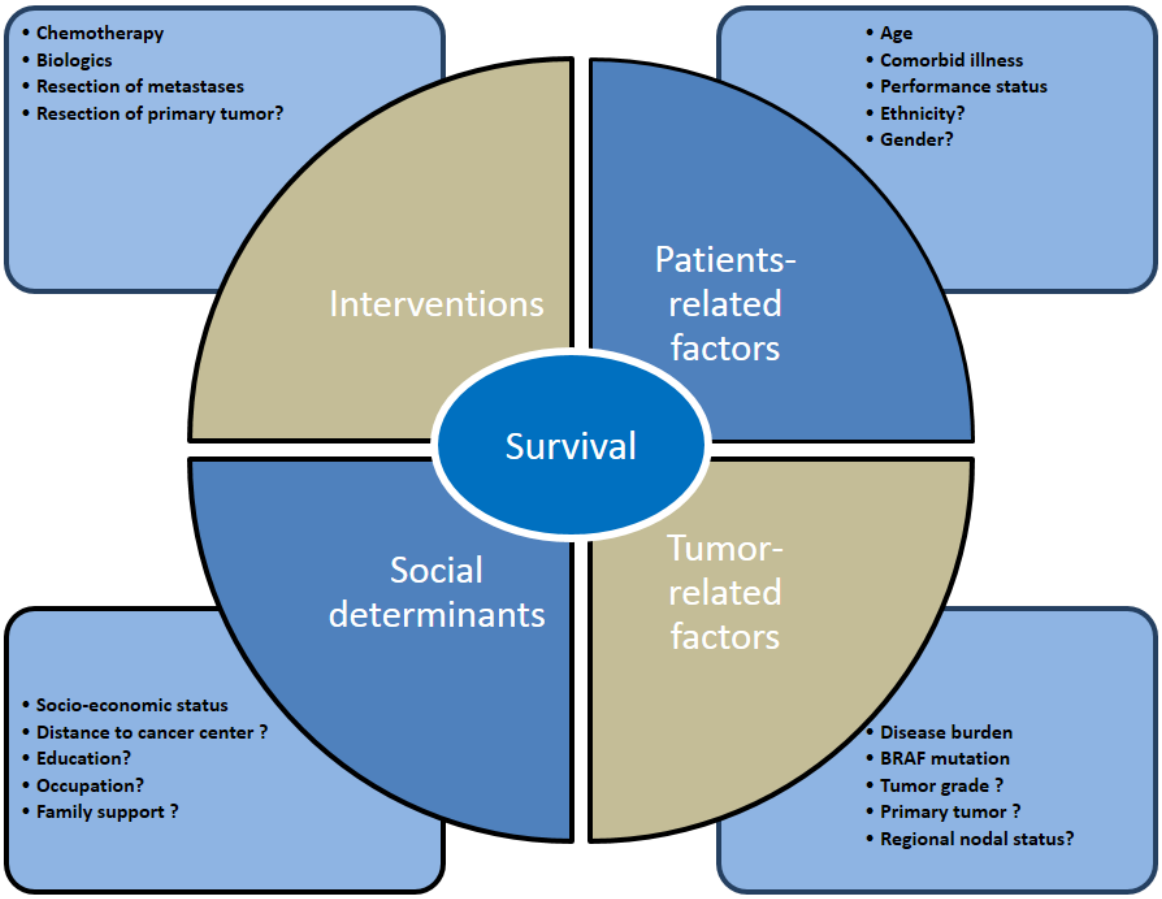
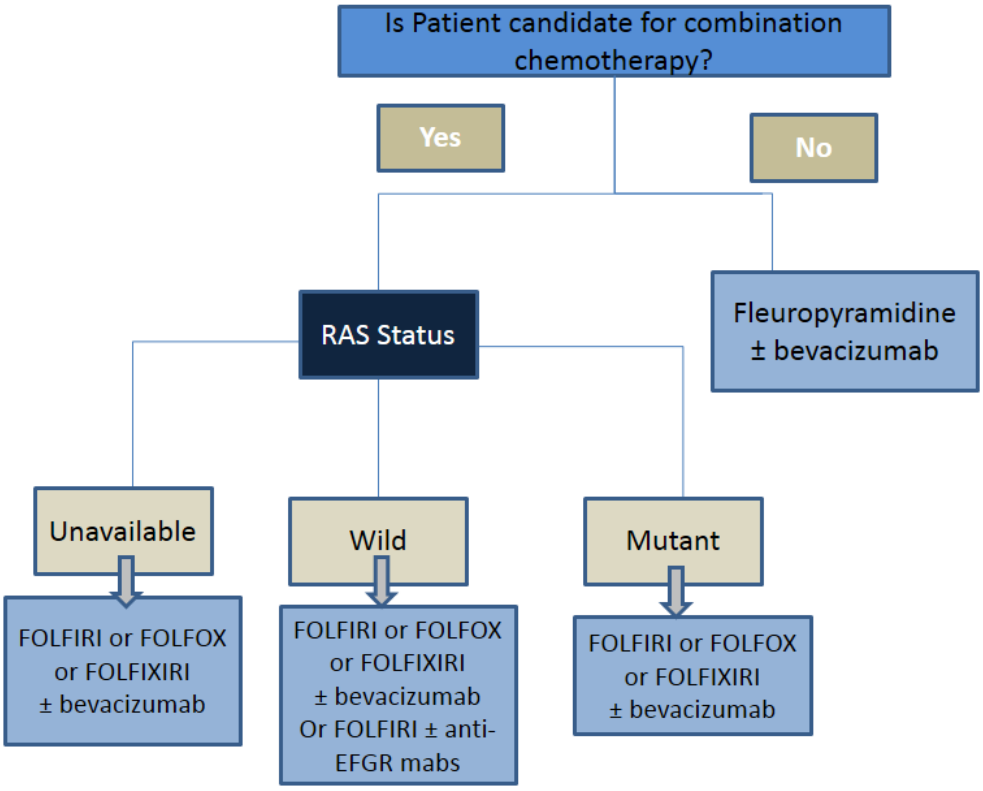


Figure 1.3: Current standard first-line combination treatments for patients with stage IV CRC and good performance status.



CHAPTER 2 - METHODS

Our research was conducted in two phases. During the first phase, we performed a systematic review of the current literature. In the second phase, we conducted population-based cohort studies to evaluate the research objectives. The present chapter focuses on research methodology. The chapter begins with the introduction of systematic review and meta-analysis, it reviews the methods used in the systematic review and meta-analysis of the literature, discusses potential advantages and limitations of a cohort study, and ends with reviewing various steps of the second phase of our research.

2.1 Systematic Review and Meta-Analysis

Systematic reviews are different from narrative reviews and address a focused question in a systematic and reproducible manner (**Table 2.1**). "A systematic review is the assembly, critical appraisal, and synthesis of all relevant studies that address a specific question incorporating strategies to minimize bias" (1, 2).

According to the Cochrane Collaboration, systematic reviews have the following features (3):

- a clearly stated set of objectives with pre-defined eligibility criteria for studies
- an explicit, reproducible methodology
- a systematic search that attempts to identify all studies that would meet the eligibility criteria
- an assessment of the validity of the findings of the studies included (e.g., thorough assessment of the risk of bias)
- a systematic presentation, and synthesis, of the characteristics and findings of the studies included

"Meta-analyses are the statistical combination of results from two or more separate studies that use statistical methods to summarize the results of independent studies" (4). A meta-analysis combines information from selected studies in a review and provide more precise estimates of effect size of the outcomes of interest than those derived from the individual studies.
A meta-analysis has following advantages (3).

1. It increases the power to detect a real effect. For example, individual studies can be small to detect small effects but, when several studies are combined there is a higher possibility of detecting a statistically significant effect if it exists.

2. The estimation of an intervention effect can be improved when it is based on more information; hence, a meta-analysis improves precision and provides a more precise estimate of an effect.

3. Meta-analyses are valuable to answer questions that are not addressed by individual studies. Most studies include specific groups of patients with explicitly defined interventions. Meta-analyses facilitate investigations of the consistency of evidence across studies and the exploration of differences across studies.

4. Meta-analyses are helpful to address controversies arising from conflicting results presented by different studies or to generate new hypotheses. Statistical analysis allows the degree of conflict to be formally assessed, and reasons for different results to be explored and quantified.

Despite potential advantages the use of statistical methods in a meta-analysis does not necessarily guarantee that the results of a review are valid.

2.1.1 Measuring Agreement in Systematic Review

In systematic reviews, many steps are done in duplicate. Calculations for agreement statistics help to determine how well the two reviewers agreed at various time-points. Agreement statistics are also used to identify problem areas, i.e., where the two reviewers interpret questions/criteria differently.

Kappa statistics are chance-corrected and represent the "standard" for reporting agreement in systematic reviews. Weighted kappa allows for partial agreement and gives 'partial credit' to partial agreement. One of the disadvantages of Kappa statistics is over-adjusts if distribution is highly skewed, i.e., very high number of positives (3).

- 0.40-0.59: fair agreement
- 0.60-0.74: good agreement
- ≥0.75: excellent agreement

2.1.2 Identifying and Measuring Heterogeneity

Heterogeneity in meta-analysis refers to the variation in study outcomes among studies (**Table 2.2**) [5-7]. A poor overlap in confidence intervals of the results of individual studies suggests presence of statistical heterogeneity. The amount of heterogeneity partly determines the difficulty in drawing overall conclusions (5,6). The chi-squared (χ^2) test is a statistical test for heterogeneity included in the forest plots (6). It assesses whether observed differences in results are due to chance alone. A low P-value provides evidence of heterogeneity and suggests that variations in effect estimates are beyond chance. Although a statistically significant result may indicate a problem with heterogeneity, a non-significant result does not necessarily exclude heterogeneity. For example, if studies have small sample size or are few in number the test have low power to detect heterogeneity. Conversely when there are many studies in a meta-analysis, the test has high power to detect a small amount of heterogeneity which clinically may not be relevant. Huggins and others have suggested that statistical heterogeneity is inevitable since clinical and methodological diversity always occur in a meta-analysis (5).

Several methods have been developed for quantifying inconsistency across studies and a useful statistic for quantifying inconsistency is I^2 (3,5,6). It describes the proportion of the variability in effect estimates from heterogeneity rather than sampling error.

$I^2 = 100\% \times (Q-df)/Q$.

Where Q is the chi-squared statistic and df is its degrees of freedom.
Thresholds for the interpretation of I^2 are usually as follows (3):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity*;
- 50% to 90%: may represent substantial heterogeneity*;
- 75% to 100%: considerable heterogeneity*.

*The importance of the observed value of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g., P-value from the chi-squared test, or a confidence interval for I^2).

2.1.3 Models for Combining Data for Meta-Analysis

In a meta-analysis results from two or more studies can be combined by using either a fixed-effect model or a random effect model (3,8-11). The fixed effect analysis assumes that all the included studies share a common effect size, μ and all factors which could influence the effect size are the same in all the study populations, and therefore the effect size is the same in all the study populations. It further assumes that the observed effect size varies from one study to the next only because of the random error inherent in each study.

The random effects model assumes that the study samples were drawn from populations that differ from each other in ways that could impact on the treatment effect. For example, the intensity of the intervention or the age of the subjects may vary from one study to the next. The model assumes that the effect size will vary from one study to the next because of random error within studies, as in the fixed effect model and due to true variation in effect size from one study to the next.

2.1.4 Objectives and Outcomes of Interest

The systematic review was performed according to the PRISMA statement guidelines (12). The review and meta-analysis "*Should Palliative Resection of Primary Tumor Be Performed in Patients with Advanced Colorectal Cancer? A Systematic Review & Meta-analysis*" is published in the Current Oncology in October 2013 (please see chapter 3) [13]. In the following section we review key elements of the research methods.

2.1.4.1 Primary Objective

- To compare survival of patients with advanced CRC who underwent primary tumor resection with patients who did not have resection.

2.1.4.2 Secondary Objectives

- To determine 30-day post-operative mortality and non-fatal complications rates in the intervention group, primary tumor complications rate in the control group, non-resection procedures and quality of life in the both groups.
- To determine survival benefit of surgical intervention in the subgroups of patients with advanced CRC who were treated with second- and third-generation anticancer therapy.
- To determine survival benefit of surgical intervention in the subgroups of relative asymptomatic or minimally symptomatic patients.

2.1.5 Methods

2.1.5.1 Definitions

- Primary tumor complication: A primary tumor complication was defined as "proportion of patients who developed bleeding, obstruction, and perforation during the study period".
- Fatal primary tumor complication: It was defined as "death within 30 days of bleeding, obstruction and perforation secondary to an intact primary tumor."
- Postoperative surgical mortality: It was defined as "death within 30 days of surgery". Non-fatal surgical complication was defined as "postoperative infection, anastomotic leak, and all other complications recorded 30 days following primary tumor resection."
- Non-resection procedures: It included bypass surgery with colostomy formation, endoscopic laser therapy or placement of endoluminal stents.
- Study utilizing second- and third-generation chemotherapy: All studies that specified the use of second- and third-generation therapy or either entire study or part of a study (≥50%) was conducted after the year 1999 were considered 'studies utilizing second- and third-generation anti-cancer therapy.'

2.1.5.2 Inclusion and Exclusion Criteria

Studies involving patients with histologically documented adenocarcinoma of colon and rectum and evidence of metastases were included. Studies with other histological diagnosis including small cell carcinoma, gastrointestinal stromal tumor (GIST), lymphoma, melanoma, anal canal cancer, and sarcoma were excluded. Only studies that have comparative data on survival (resection vs. a non-resection group) were included. Studies involving groups with upfront metastasectomy, curative resection, or with non-surgical procedures were excluded. The inclusion criteria were specified using the PICO (population, intervention, comparison, outcome) format (please also see **Appendix A**).

- Study Population
  - Patients with advanced adenocarcinoma of the colon and rectum
- Intervention
  - Surgical resection of the primary tumor
- Control group
  - no surgery
- Outcome of interest

- Primary outcome of interest: overall survival.
- Secondary outcomes of interest: postoperative mortality and morbidity, complications rate of the primary tumor, non-surgical interventions in the control group, and quality of life.

- Research design.
- Randomized controlled trial, controlled trials, cohort studies (prospective & retrospective), and case control studies.

2.1.5.3 Information Sources

An extensive literature search was performed using the Medline (Ovid interface; version 1946 to February 2012), EMBASE (Ovid interface; version 1947 to February 2012) and CENTRAL (The Cochrane Central Register of Controlled Trials, The Cochrane Library, Wiley, Issue 3 2012) by using a pre-specified protocol. In addition, grey literature (the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) clinical practice guidelines, education books, the National Comprehensive Cancer Network (NCCN) guidelines) was reviewed for relevant studies. Flow of information through the different phases of literature search was recorded. Studies were selected by using pre-specified criteria with restriction to publication dates from January 1980 till May 2012, English language, and human studies (**Appendix A**).

2.1.5.4 Search Strategies and Selection of Studies

Literature search was performed in three stages. In the first stage**,** MEDLINE & EMBASE were searched for the relevant studies. All relevant studies were identified using the first 3 components of PICO format. Studies comparing survival of patients with advanced CRC who underwent primary tumor resection with patients who did not have surgery were included.
Following concepts were used:

- Advanced colorectal cancer
- Surgery

We conducted a pilot search after consulting a health science librarian; various key words and controlled vocabulary (for different concepts) were used utilizing ‘explode’ and ‘focus’ (for controlled vocabulary) in various combination. Because of the use of ‘explode’ revealed mostly irrelevant articles, for the final search ‘explode’ and ‘focus’ were not utilized. Likewise, use of the key word “advanced colorectal cancer” with its synonyms only retrieved small number of articles. In order to increase the search sensitivity, the term “Advanced colorectal cancer” was entered separately as “advanced” AND “colorectal cancer”.

The following keywords, synonyms, and controlled vocabulary (MESH & EMTREE) were used: ‘‘colorectal cancer’’ or ‘‘colon cancer’’ or ‘‘rectal cancer’’ or ‘‘colorectal neoplasm’’ or “colon neoplasm” or “rectal neoplasm” (Please see the **Appendix B** for search terms)
“advanced” or “stage IV” or “stage 4” or “stage four” or “metastatic”…..
“surgery” or “colorectal surgery” or ‘‘palliative surgery” or “palliative surgery” or “surgical removal.”

The three sets of terms were joined together with the ‘AND’ operator. Studies were selected using pre-specified criteria with restriction to publication dates since 1980, English language, and human studies. The title and abstract of the searched articles were reviewed to identify relevant studies. In addition, further studies were identified using ‘similar study’. All relevant citations were exported to the Refwork.

In the second stage CENTRAL was searched using the term “colorectal cancer" or "colon cancer" or rectal cancer" or “colorectal neoplasms” and “surgery”. In order to increase the search sensitivity the term “advanced” or “Stage IV” were avoided.

In the third and final stage of the search, the grey literature including education material from scientific proceedings and current practice guidelines in the management of colon and rectal cancer by ASCO, ESMO and NCCN were reviewed. Citation index was used to identify relevant articles in that subject.

Based on the initial search results, two investigators independently evaluated the abstracts and selected the relevant articles matching the selection criteria. The Cohen’s kappa statistics was used to assess agreement between the two investigators on the selection of articles (14). All the subsequent related studies-hand search was performed by the primary investigator.

The keywords, synonyms, and controlled vocabulary (MESH & EMTREE) that were used for the literature search are described in detail in the **Appendix A & Appendix B**. Due to lack of controlled trial addressing this question our search strategy included studies of all designs.

The computerized literature search was augmented by manual review of citations of the relevant studies to identify additional articles for assessment. The reference lists of retrieved articles, review articles and clinical practice guidelines were reviewed for identification of additional studies. Original publications were selected if the abstract contained safety and efficacy data of patients with and without primary tumor resection. In case of duplicate publications, the most recent and/or most complete studies were included.

Two authors examined all citations and abstracts derived from the electronic search strategy and independently selected the articles to be included in the review. A standardized form was used for full text screening to assess eligibility of studies for inclusion in the review (**Appendix C**). The Cohen’s kappa was used to assess agreement between investigators for the full-text screening of studies for inclusion. Any disagreement between the reviewers was resolved by discussion.

2.1.5.5 Data Collection

The data extraction form was used to extract and record information on the results of included studies. It was piloted by a preliminary search and after discussion a final extraction form was developed. Two authors independently extracted the data. Results were compared between reviewers. Disagreements were resolved by discussion.

The following data was extracted from included studies: study eligibility, design and characteristics, funding source, baseline patients characteristics (age, gender, co-morbid illnesses, Eastern Cooperative Oncology Group (ECOG) performance status [**Table 2.3**], etc.), primary tumor location, disease burden (extent of liver involvement, extra-hepatic disease, etc.), co-interventions (radiation therapy, chemotherapy, second- and third-generation chemotherapy, metastasectomy rate, etc.), and primary and secondary outcomes (median overall survival, 30-day postoperative mortality, primary tumor complications, non-surgical procedures, and quality of life [**Appendix D**]). For relevant missing information attempts were made to contact the corresponding authors of all the eligible studies. A manual was written to clarify the electronic data abstraction sheet and to reduce the disagreement between the data extractors (**Appendix E**).

2.1.5.6 Validity Assessment

Study designs were evaluated according to the following: retrospective or prospective, and randomized or observational. Two authors independently evaluated all included studies using a list of selected quality items assessing components of validity and bias. Disagreements were resolved by discussion. The assessment of risk of bias for eligible studies was conducted by each reviewer using guidelines in the Cochrane Handbook for Systematic Reviews of Interventions. For randomized controlled trial the elements of risk of bias assessment included quality of random allocation and concealment, blinding' during treatment and at outcome assessment, description of dropouts and withdrawals, analysis by intention to treat, and other bias such as early stopping, baseline imbalance, source of funding (3). For observational studies we applied "the Newcastle-Ottawa Quality Assessment Scale (NOS)" [15]. The Newcastle-Ottawa score consists of nine items grouped in three sections that are relevant for high quality of an observational study. For cohort study these items are as follow (**Appendices F1 & F2**). *Selection*: (1) true representativeness of the exposed cohort in the community, (2) non exposed cohort drawn from the same community, (3) ascertainment of exposure, and (4) demonstration that outcome of interest was not present at start of study. *Comparability of cohorts*: (5) control for symptoms and (6) control for systemic therapy. *Outcome*: (7) assessment of outcome, (8) follow–up was long enough for outcomes to occur and (9) adequacy of follow up of cohorts. Please see **Appendices F1-3** for further detail and items for case control study.

For each outcome of interest validity scores were evaluated as follows: $\leq$ 5: low quality; 6-7 medium quality; 8-9 high quality (15). The Cohen's kappa statistics was used to assess agreement between the two investigators on the outcomes of interest (14).

2.1.5.7 Analysis & Synthesis of Result

The results of the studies included were combined to evaluate primary outcome in a formal meta-analysis to produce an overall estimate of surgical intervention. For a quantitative pooling the DerSimonian and Laird random effects model of meta-analysis was used using RevMan analysis software (RevMan 5.1.2) of the Cochrane Collaboration RevMan software (16). Treatment effects were expressed as hazard ratios (HR) with corresponding 95% confidence intervals (CI). For studies that have not provided numeric information about time to event, HR and variance were estimated using Kaplan-Meier survival curves (17). A P-value of 0.05 was used as the cut-off value to determine statistical significance. Funnel plots were constructed to evaluate potential publication bias. Heterogeneity across studies was assessed using statistical test and the proportion of variation was expressed as $I^{2.}$ All other outcomes were presented in a descriptive way and results were presented as mean or median of all variables in the analyzed studies. Single group analyses were done for surgical mortality and complications rate (intervention group) and primary tumor complication rates (control) as these outcomes were not applicable to the comparator group. Sensitivity analyses were performed if appropriate. Pre-specified subgroup analyses were performed to assess survival of patients with relatively asymptomatic or minimally symptomatic primary tumor and studies involving patients treated with second- and third-generation anticancer therapy. Minimal symptoms included abdominal discomfort, weight loss, and occult blood loss. Risk of bias for all outcomes across studies was done in duplicate by the two reviewers and was reported using the GRADE scale (18).

The results and some of the limitations of the systematic review and meta-analysis are discussed in the next chapter.

2.2 Cohort Study

Observational studies are an important category of study designs (19). There is evidence that well-designed observational studies have provided comparable results to randomized controlled trials (RCT) in many instances (19-21). For example, Benson and Hartz evaluated 136 studies in 19 treatment areas. The estimates of the effects of treatment in observational studies and in RCTs were similar in most areas, and for only 2 of the 19 treatments, the magnitude of the effect in the combined observational studies were outside the 95 percent confidence interval for the combined RCTs. Observational studies can also complement RCTs in hypothesis generation, establishing questions for future RCTs, and defining clinical conditions (19).

Cohort studies and case-control studies are two primary types of observational studies that aid in evaluating associations between exposures (interventions) and diseases (outcomes). Cohort studies are observational studies that compare the subsequent occurrence of illness, injury, or death among groups of people whose exposure status differs “naturally”, i.e. not as a result of random assignment (22). A cohort is defined as a “group of people with defined characteristics who are followed up to determine incidence of, or mortality from, some specific disease, all causes of death, or some other outcomes” (23). Cohort studies can be prospective or retrospective.

Prospective studies are carried out from the present time into the future. In retrospective cohort studies, a cohort of subjects is selected at the present time based on exposure status; event status, which was measured in the past, is reconstructed for analysis (22,23). A characteristic of cohort study is that both the exposed and unexposed groups are selected from the same source population. While a closed cohort enrolls a defined number of participants at study onset and follows them from that time forward, in open cohorts the study population is dynamic and people enter and leave the population at different points in time (22).

Poor reporting of observation studies can affect the assessment of the strengths and weaknesses of a study and the generalizability of its results. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) group has established guidelines on reporting observational research to improve the transparency of the methods, thereby facilitating the critical appraisal of a study's findings (24,25). Cohort studies are less prone to selection bias compared to case-control studies.

2.2.1 Study Design

Retrospective cohort study.

2.2.2 Study Population

Patients with synchronous metastatic CRC diagnosed between the period of 1992 and 2010 in the province of Saskatchewan, Canada. Survival benefit of primary tumor resection was evaluated initially in a patient cohort diagnosed during the period of 1992 to 2005. The findings were validated in a second cohort of patients diagnosed from 2006 to 2010.

2.2.3 Eligibility Criteria

2.2.3.1 Inclusion Criteria

- Histologically documented adenocarcinoma of colon and rectum and evidence of metastases.
- Age at least 18 years.
- No other active secondary malignancy.

2.2.3.2 Exclusion Criteria

- Patients with other histological diagnosis including small cell carcinoma, gastrointestinal stromal tumor (GIST), lymphoma, melanoma, anal canal cancer, melanoma and sarcoma were excluded.
- Patients with fixed un-operable primary tumor.

2.2.4 Definitions

Major comorbid illnesses were defined as the presence of coronary artery disease, congestive heart failure, diabetes mellitus, chronic renal insufficiency, uncontrolled hypertension, peripheral vascular disease, stroke, chronic obstructive lung disease, interstitial lung disease, connective tissue disease, dementia, symptomatic multiple sclerosis, cirrhosis of the liver, mental illnesses (depression, bipolar disorder, schizophrenia, anxiety disorders, and others) and AIDS among others. The Charlson Comorbidity Index was used in the validation study to defined major comorbid illness (26, 27). It is a method to categorize comorbidities of patients based on the International Classification of Disease (ICD) diagnosis codes. The original index and the weights for the index have been modified (28, 29). The higher the score the more likely the predicted outcome will result in mortality. The asymptomatic or minimal symptomatic disease was defined as absence of obstruction, perforation or bleeding. Postoperative mortality was defined as death that occurred within 30 days of surgery. Second generation therapy was defined as use of bevacizumab or anti-epidermal growth factor receptor antibodies cetuximab or panitumumab and/or oxaliplatin or irinotecan based therapy (FOLFOX or FOLFIRI).

The site of the primary tumor was classified as right colon (located between the cecum through to the transverse colon), transverse colon, left colon (from the splenic flexure to the sigmoid colon), sigmoid colon, or rectal (within 15 cm of the anal verge) or recto-sigmoid (involvement of both rectum and sigmoid colon). Sites of distant metastasis are categorized as follows: liver or extra-hepatic which include lung, bone, brain, peritoneum (including malignant ascites diagnosed by cytology), and others such as distant lymph nodes (including supraclavicular, mediastinal, inguinal, conglomerated retroperitoneal, and para-aortic lymph nodes), spleen, pancreas, kidneys, and skin.

2.2.5 Data Source

One of the advantages of population-based cancer registries is that outcome can be determined for the entire population. Saskatchewan is home to one of the world's oldest cancer registries. The Saskatchewan cancer registry is a population-based registry and information system, which is designed for the collection, management, and analysis of data for residents diagnosed with cancer in the province. The database is prospectively collected and updated. There are currently approximately 226,800 patients on the database. Using the Saskatchewan Cancer Registry patients with Stage IV CRC diagnosed between the period of 1992 and 2005 were identified. The following ICD codes were used to retrieve the medical records (ICD).

C18.0 cecum and ileocecal valve, C18.1 appendix, C18.2 ascending colon, C18.3 hepatic flexure, C18.4 transverse colon, C18.5 splenic flexure, C18.6 descending colon, C18.7 sigmoid colon and sigmoid flexure, C18.8 overlapping lesion of colon, C18.9 colon include large intestine not otherwise specified, C 19 malignant neoplasm of rectosigmoid junction include colon with rectum and rectosigmoid colon, C 20 malignant neoplasm of rectum include rectal ampulla (30).

For the purpose of accuracy in the staging and histopathology, individual records of patients diagnosed with all stages of CRC (stage I, II, III, and IV) were retrieved. All records were reviewed

manually for eligibility criteria. Stage IV or metastatic CRC is comprised about 20% of all cases of newly diagnosed CRC. Hence, this study required review of more than 10,000 individual patients' records.

The study period is chosen due to the fact that in early the 1990s palliative chemotherapy became available for patients with advanced CRC and in the year 2000, second-generation therapy (irinotecan and oxaliplatin) and subsequently third-generation therapy (biological treatment) became available for patients with advanced CRC in the province of Saskatchewan. Individual medical records of all patients diagnosed with CRC during the study period were reviewed for accuracy in staging and histology. All patients were followed until their death or until June 2014 when the data entry was closed.

2.2.6 Data Collection

The following data were extracted from the individual patient record by a trained research associate. Baseline patients characteristics (age, gender, co-morbid illnesses, Eastern Cooperative Oncology Group (ECOG) performance status, smoking status), primary tumor location (right colon, left colon, rectum), disease burden (liver involvement, extra-hepatic disease including lung and peritoneum), co-interventions (radiation therapy, chemotherapy, second- or third-generation chemotherapy, metastasectomy rate), pathology (grade, mucinous histology), laboratory test (hemoglobin, white blood cell counts, platelets counts, sodium, creatinine, bilirubin, albumin, carcinoembryonic antigen (CEA) levels), and primary and secondary outcomes (median overall survival, 30-day post-operative mortality, 30 days post-operative morbidity, non-resection surgical procedures) (**Appendices G & H**). Performance status information was collected using ECOG scale. If the performance status was recorded using the Karnofsky performance status score, it was transformed into ECOG scale as described in the **Appendix I**.

2.2.7 Statistical Consideration and Data Analysis

2.2.7.1 Sample Size

Since a high rate of primary tumor resection has been reported in the literature, assuming two thirds of patients in Saskatchewan underwent resection of primary tumor, a ratio of 1:2 was used for non-resection group versus resection group. Using a power of 90%, type 1 error of 0.05 with 2 sided P-value, and survival difference of 20% in the two groups (resection vs. non-resection) with a follow-up period of 60 months, a total sample size of 959 patients was estimated (326 in the non-resection group and 633 patients in the resection group) [**Appendix J**].

2.2.7.2 Demographic and Baseline Characteristics

Descriptive statistics are provided to summarize the studied population demographics and baseline characteristics parameters. Categorical data were summarized as frequency and its corresponding proportion. For continuous data frequency, median, minimum, maximum, mean (as appropriate), and standard deviation are provided for each parameter. The chi-square test and Student's t-test were performed for analysis of categorical and continuous variables.

2.2.7.3 Survival Analysis

Survival analyses were performed to assess primary and secondary endpoints. Survival analysis typically focuses on time to event data (31). In survival analysis, subjects are usually followed over a specified time period and the focus is on the time at which the event of interest occurs (31-34). Observations are called censored when the information about their survival time is incomplete. Three reasons of censoring are: when a person does not experience the event before the study ends, when a person is lost to follow-up, and when a person withdraws from the study (35). A non-informative and random censoring is required to avoid bias in a survival analysis. The survival data has the following features: 1) the outcome variable, the time to a well-defined event and the status of the event; 2) censored observations, if the event of interest has not occurred at the time of data analysis; 3) the predictors or explanatory variables that could potentially influence the outcome variable (31).

The survival and hazard functions are key elements in survival analysis for describing the distribution of event times. The survival function S (t) is fundamental to a survival analysis. It gives the probability that a person survives longer than some specified time *t* and that the random variable T exceeds the specified time t (31-35). The hazard function h (t) gives the instantaneous potential per unit time for the event to occur, given the individual has survived up to time *t* whereas the hazard ratio is an estimate of the ratio of the hazard rate in the treated versus the control group (36). The hazard rate is the probability that if the event in question has not already occurred, it will occur in the next time interval, divided by the length of that interval. The time interval is made very short, so that in effect the hazard rate represents an instantaneous rate.

The hazard function – denoted by h (t) – can be estimated using the following equation:
h (t) = number of individuals experiencing an event in interval beginning at t/ (number of individuals surviving at time t) x (interval width).

There are three primary goals of survival analysis, to estimate and interpret survival and / or hazard functions from the survival data; to compare survival and / or hazard functions, and to assess the relationship of explanatory variables to survival time (31).

Unlike ordinary regression models, survival methods correctly incorporate information from both censored and uncensored observations in estimating important model parameters. There are three main approaches to analyze the relationship of a set of predictor variables with the survival time: nonparametric, parametric, and semi-parametric (31,33). Nonparametric methods provide simple and quick looks at the survival experience. The Kaplan-Meier method, a nonparametric estimator of the survival function, is widely used to estimate and graph survival probabilities as a function of time (37). Parametric methods assume that the underlying distribution of the survival times follows certain known probability distributions. Popular parametric methods include the exponential, Weibull, and lognormal distributions (31). The Cox regression model is a semi-parametric model which unlike parametric models, makes no assumptions about the shape of the so-called baseline hazard function. The Cox proportional hazards regression model remains the dominant survival analysis method to test for differences in survival times of two or more groups of interest, while adjusting for covariates of interest.

2.2.7.3.1 The Kaplan–Meier Method

Survival of the study cohorts were estimated by using the Kaplan-Meier (KM) method. The KM survival curve is defined as "the probability of surviving in a given length of time while considering time in many small intervals" (37). The KM estimate is also called as "product limit estimate". In KM the time is divided into periods of fixed length and each period or segment is the interval between two non-simultaneous terminal events. In addition, in each segment, calculation is made of the probability of survival as the product of the probability of survival at the start of the interval and the probability of survival at the end of the interval – since the subject was alive at the start (31,33,37). In KM three assumptions are made: at any time subjects who are censored have the same survival prospects as those who continue to be followed, the survival probabilities are the same for subjects recruited early and late in the study, and the event happens at the time specified.

2.2.7.3.2 The Log-Rank Test

The survival distributions of different groups were compared by the log-rank test. The log-rank test is a form of chi-square test and is used to test the null hypothesis that there is no difference between the populations in the probability of an event at any time point (31,35,38). The analysis is based on the times of events. The log-rank test is based on the same assumptions as the Kaplan Meier survival curve that censoring is unrelated to prognosis and the survival probabilities are the same for subjects recruited early and late in the study, and the events happened at the times specified. The test is more likely to detect a difference between groups when the risk of an event is consistently greater for one group than another. The log-rank test is purely a test of significance and cannot provide an estimate of the size of the difference between the groups (38). Furthermore, the log-rank test cannot be used to explore and adjust for the effects of prognostic variables, such as age and disease duration, known to affect survival.

2.2.7.3.3 The Cox Proportional Hazards (PH) Model

There are several known variables that can affect the survival of patients with Stage IV CRC. These variables include age, comorbid illnesses, performance status, extent of cancer and systemic therapy (39-41). Furthermore, pretreatment hematologic abnormalities have been reported to have prognostic value in patients with solid tumors (42, 43). We performed multivariate analyses to determine the prognostic significance of the primary tumor resection in patients with Stage IV CRC. The Cox proportional hazard model was used and the hazard ratios and 95% confidence limit were estimated.

The Cox proportional hazards model is a popular mathematical model that is both powerful and flexible for the analysis of survival data (31,33,44,45). Cox regression is considered a 'semi-parametric' procedure because the baseline hazard function, $h_0(t)$, does not have to be specified. In this model, the relative risk is described parametrically and the hazard functions non-parametrically. The model simultaneously explores the effects of several variables on survival and allows the researchers to isolate the effects of treatment from the effects of other variables. It provides an estimate of the hazard ratio and its confidence interval and may improve the estimate of treatment effect by narrowing the confidence interval.

The Cox proportional hazard model makes assumptions that the hazard ratios of two people are independent of time, and are valid only for time-independent covariates and that the hazard functions for any two individuals at any point in time are proportional (31). In other words, if a person is at risk of death at some initial time point that is twice as high as that of another person, then at all later times the risk of death remains twice as high.

Cox's method is similar to multiple regression analysis, except that the dependent (Y) variable is the hazard function at a given time. If there are several explanatory (X) variables of interest such as age, gender, interventions, then the hazard or risk of dying at time t can be expressed as (31):

$$h(t) = h_0(t)\exp(\beta_{age} \times age + \beta_{gender} \times gender + \cdots + \beta_{group} \times group)$$

Taking natural logarithms of both sides:

$$\ln h(t) = \ln h_0(t)\exp(\beta_{age} \times age + \beta_{gender} \times gender + \cdots + \beta_{group} \times group)$$

The quantity h0 (t) is the baseline or underlying hazard function and corresponds to the probability of death when all the explanatory variables are zero. The regression coefficients β_{age} to β_{group} give the proportional change that can be expected in the hazard, related to changes in the explanatory variables.

The proportional hazards assumption can be tested using graphical, goodness of fit test and time-dependent covariates (31). For example, with complementary log-log plot, if the hazards are proportional across the group, a plot of the logarithm of the negative logarithm of the estimated survivor function against the logarithm of survival time will yield parallel curves. Parameter (β) estimates in the Cox PH model are obtained by maximizing the partial likelihood (45). Cox and others have shown that this partial log-likelihood can be treated as an ordinary log-likelihood to derive valid (partial) maximum likelihoods of β (44,45).

In our cohort studies we examined the following variables with respect to their prognostic significance: *Interventions*: Resection of primary tumor, metastasectomy, use of chemotherapy, second generation chemotherapy, second-line therapy, third-line therapy, and radiation therapy; *clinical & demographic variables*: age, gender, major comorbid illness, secondary cancer, ECOG performance status, cancer center, and active smoking; *laboratory values*: albumin, bilirubin, alkaline phosphatase, sodium level, serum creatinine, blood urea nitrogen (BUN), hemoglobin, white blood cell (WBC), platelet count, and carcinoembryonic antigen (CEA); *disease characteristics*: site, grade, mucinous tumor, symptomatic disease, extra-hepatic metastases, and stage.

Following cutoffs were used to categorize continuous variables. age (<65 vs. ≥65) or (<70 vs. ≥70), albumin (≥36 vs. <36 g/l), bilirubin (≥26 vs. <26 um/l), alkaline phosphatase (≥120 vs. <120 mm/l), sodium level (≤135 mEq/l vs. >135 mEq/l), serum creatinine (≥120 vs. <120 um/l), BUN (≥8 vs. <8 mm/l), hemoglobin (≥120 vs. <120 g/l), WBC (≥11 vs. <11 x 10^9/l), platelet count (≥450 vs. <450 x10^9/l), and CEA (≥6 vs. <6 mcg/l). The categorical or ordinal variables were characterized as: site (colon vs. rectal), grade (3 vs. <3), and stage (Stage IVa vs. Stage IVb disease).

For the patients cohort that underwent surgical resection of the primary tumor , tumor-related characteristics including nodal status, T status, the ratio of metastatic to examined lymph node (LNR) [median number was used as a cutoff value] and number of lymph nodes removed (≥12 vs. r <12) were examined in a multivariate analysis. For the Cox proportional hazard model, the proportional hazards assumption was assessed for the variables using the log-log survival curves. All variables that were significant on univariate analysis with P<0.05, were examined in multivariate models. The likelihood ratio test and *t* test were used to determine if a variable correlates with survival in the model. Tests for interaction were performed for surgery and the other prognostic variables that were correlated with survival. In addition to the tests for interaction, secondary analyses were performed in subgroups of patients with asymptomatic or minimally symptomatic disease, patients who did not have metastasectomy, and patients who were treated with combination chemotherapy. A two-sided P-value of <0.05 was considered to be statistically significant. For missing data an imputation technique was used. The SPSS version 21-22 and the STATA MP version 13.1 (StataCorp College Station, TX) were used for statistical analysis (SPSS Inc. Chicago, IL).

2.2.7.4 The Logistic Regression

In our one of companion studies we used logistic regression method to assess the relationship between the use of chemotherapy and various variables in patients with newly diagnosed stage IV CRC. Regression methods are important to describe the relationship between a response variable and predictor variables (46). The logistic regression model has its basis in the odds of a two-level outcome of interest. The ratio of odds of disease in exposed individuals relative to the unexposed is called the odds ratio (47). Logistic regression analysis is a multiple regression technique that can be applied in research situations where the outcome variable is categorical. The logistic regression model takes the natural logarithm of the odds as a regression function of the predictors (48). With 1 predictor, X, this takes the form ln [odds(Y=1)] $=\beta_0+\beta_1 X$, where ln stands for the natural logarithm, Y is the outcome and Y=1 when the event happens (versus Y=0 when it does not), β_0 is the intercept term, and β_1 represents the regression coefficient, the change in the logarithm of the odds of the event with a one-unit change in the predictor X (46).

The goal of the regression analysis is to find the best fitting and most parsimonious, yet biologically reasonable model to describe the relationship between an outcome and a set of independent variables. The method of parameter estimation is maximum likelihood. The likelihood function expresses the probability of the observed data as a function of the unknown parameters. The maximum likelihood method is used to produce estimators that are consistent, asymptotically (for large *n*) efficient and asymptotically normal (46). The logistic regression modeling approach is based on the concept of logistic function.

However, if the model and the data are not in good agreement, then these odds ratios are not very meaningful (48, 49).

2.2.7.5 Area-level Variables

Few Canadian vital statistics include socio-economic data that would facilitate identification of disparities in the outcomes of cancer patients. Furthermore, most health system-generated data and disease registries lack socio-economic content. Hence, it is challenging to assess relationship between various social determinants of health and survival of newly diagnosed Canadian patients with stage IV CRC. Area-based socio-economic measures utilize information to characterize the socio-economic profile of geographic areas rather than of individuals. They serve as proxy for individual-level characteristics. Greater homogeneity within areas signifies greater reliability of this proxy status of the area data for micro-level data (50). Area-level socioeconomic status can be obtained by matching individuals to a spatial location using place of residence information such as postal codes.

There is evidence that area-level indicators of socioeconomic status predict health outcomes independent of the individual-level variables (51-54). There are associations between area-level socioeconomic status (SES) and colorectal cancer. For example, lower area-level SES has been associated with higher risk of colorectal cancer (55-57). It is important to recognize the extent to which observed associations between area-level SES and cancer outcomes are due to compositional factors such people living in lower-SES areas are themselves of lower SES with an increased risk of mortality or potentially influenced by contextual factors such as physical environment, and neighborhood resources, which may contribute to inferior outcomes independent of individual SES. This information can be very useful for appropriate interventions to reduce socioeconomic disparities (58, 59).

2.2.7.5.1 Frailty Model

A frailty model is a random-effects model, where the random effect (the frailty) has a multiplicative effect on the hazard function of an individual or a group or cluster of individuals (60). Frailty is a random component designed to account for variability due to unobserved individual-level factors that is otherwise unaccounted for by the other predictors in the model (31).

2.2.7.5.2 Shared Frailty Models

In the shared frailty model, individuals j in a group i are supposed to share the same frailty Z_i. The conditional hazard for individual j in group i is:

$\lambda(t_{ij}|Z_{ij}) = Z_i\lambda(t_{ij})$ where $\lambda(t_{ij}) = \lambda_0(t_{ij})\exp(\beta X_{ij})$ in the Cox-regression model.

The interpretation of this model is that the between-group variability (the random variation of Z) leads to different risks for the groups, which then show up as dependence within the group. Small value of θ reflects a greater degree of heterogeneity among groups and a stronger association within groups and large value of θ corresponds to the case of independence.

In an exploratory analysis we evaluated prognostic significance of area level variables in the patients' cohort (2006-2010) who were treated with modern chemotherapy. The postal code

information was obtained for all individuals. The Census subdivision information was retrieved using the Postal Code Conversion File (PCCF) [61]. PCCF is a digital file which provides a correspondence between the Canada Post Corporation (CPC) six-character postal code and Statistics Canada's standard geographic areas (Census subdivisions) for which census data and other statistics are produced (62). About 94% of the postal codes were linked to geographic areas using the new automated process.

In the profile of the 2006 census subdivisions (Canadian Census Analyzer) information about total population, population of certain races and minorities, income, the level of education among others for all provinces, divisions and subdivisions are available.

Cox models with shared frailty were fitted. The individual clinicopathological variables that demonstrated correlation with survival in a multivariate Cox Proportional Hazard model were used in the model. Following area level variables were examined with respect to their correlation with overall survival. Household income, family income, age dependency ratio, unemployment rate, aboriginal population, high school certificate, single parent, and minority. In addition, we used socio-economic Factor Index 2 (SAFEI 2). The SAFEI 2 includes four variables from the census: average household income, proportion of high school graduates, unemployment rate, and proportion of single-parent families (63, 64). The contribution of a variable to the factor is known as a factor loading and can range from -1 to +1. The larger the absolute size of the loading, the more important that variable is for the factor. All variables were categorized by using their mean values as a cutoff point. In addition, the variables were also examined using their quartiles (**Table 1**). The result is provided in the Appendix **K**.

In the following sections we reviewed the results of our research projects using the draft of the manuscripts published in the peer reviewed journals. The lead author made major contributions to concept and design, data analysis, interpretation, drafting and revising the manuscripts and correspondence. In the Appendices **L** and **M**, certificate of ethics approval and permission to reproduce the articles, are provided, respectively.

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Table 2.1: Comparison of systematic and narrative reviews.

Characteristics	Narrative Review	Systematic Review
Question	General or non-existent	Focused question using PICO (population, intervention or exposure, comparison and outcomes of interest)
Literature Search	not specified or if reported not a comprehensive search	Explicit and comprehensive search of several evidence sources
Selection of studies	Not specified or if reported potentially biased sample of selected studies	Explicit eligibility criteria for inclusion and exclusion of studies
Assessment of validity	Seldom reported and if reported are not systematic	Rigorous methodological assessment of risk of bias of reported studies
Summary of results	Qualitative non-systematic summary	Qualitative or quantitative synthesis of findings of studies are systematic

Table 2.2: Source of heterogeneity in meta-analyses.

Character	Real	Artefactual
Population	Disease severity, co-morbidity, age and gender	Improper randomization, differential follow up
Intervention	Time, duration, dose	Non-compliance, cross over
Co-intervention	Therapy, drugs	Undetected co-interventions
Outcome	Timing of outcome, event type	Differential error, non-differential error

Table 2.3: Eastern Cooperative Oncology Group (ECOG) or World Health Organization (WHO) performance scale.

Performance status	Definition
0	Fully active; no performance restrictions
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
2	Capable of all self-care but unable to carry out any work activities. Up and about >50 percent of waking hours.
3	Capable of only limited self-care; confined to bed or chair >50 percent of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

CHAPTER 3 – SYSTEMATIC REVIEW AND META-ANALYSIS OF THE PUBLISHED LITERATURE

The following four chapters are comprised of four manuscripts and summaries of the results. The manuscripts address the results of the primary research objectives. The first manuscript systematically reviews the published literature and synthesizes the data in relation to primary tumor resection in stage IV CRC. It discusses the limitations of the results. The second paper describes the results of our population based cohort study, in a cohort of patients with synchronous metastatic CRC, diagnosed from January 1992 to December 2005. The third paper reviews the survival benefit of primary tumor resection in a sub-cohort of patients with asymptomatic or minimally symptomatic primary tumor. The final paper validates the research findings in a cohort of patients with synchronous metastatic CRC, diagnosed from January 2006 to December 2010.

The present chapter addresses the study objective "to systematically review the published literature and synthesize the data in relation to primary tumor resection in stage IV CRC" and reviews the published literature till February 2012. The study findings were presented in September 2012 at the European Society of Medical Oncology (ESMO) Annual Meeting in Vienna, Austria and in June 2013 at the American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, USA in the poster sessions. The results were published in the Current Oncology "*Ahmed S, Shahid RK, Leis A, Haider K, Kanthan S, Reeder B, Pahwa P. Should non-curative resection of primary tumor be performed in patients with stage IV colorectal cancer? A systematic review & meta-analysis. Current Oncology 2013 Oct; 20(5):e420-41*".

3.1 Abstract

Purpose: Surgical resection of the primary tumor in patients with advanced CRC remains controversial. This review compares survival in patients with advanced CRC who underwent surgical resection of the primary tumor with that in patients not undergoing resection, and determines postoperative mortality & nonfatal complications rates, primary tumor complication rate (PTCR), the non-resection surgical procedures rate (NSPR) and quality of life (QOL).

Patients and Methods: Reports in the CENTRAL, Medline, and EMBASE databases were searched for relevant studies, which were selected using pre-specified eligibility criteria. The search was also restricted to publication dates from 1980 onward, the English language, and studies involving human subjects. Screening, evaluation of relevant articles, and data abstraction were performed in duplicate, and agreement between the abstractors was assessed. Articles that met the inclusion criteria were assessed for quality using the Ottawa-Newcastle Scale. Data were collected and synthesized per protocol.

Results: From among the 3379 reports located, fifteen retrospective observational studies were selected. Of the 12456 patients in the selected studies, 8620 (69%) underwent surgery. Median survival was 15.2 months (range: 10-30.7) in the resection group and 11.4 months (range: 3-22) in the non-resection group. Hazard ratio for survival was 0.69 (95% CI: 0.61-0.79) favoring surgical resection. Mean rates of postoperative mortality and nonfatal complications rates were 4.9% (95% CI: 0-9.7) and 25.9% (95% CI: 20.1-31.6) respectively. The mean primary tumor complications rate was 29.7% (95% CI: 18.5-41.0), and the non-resection surgical procedures rate in the non-resection group was 27.6% (95% CI: 15.4-39.9). No study provided QOL data.

Conclusions: Although this review supports primary tumor resection in advanced CRC, the results have significant biases. Randomized trials are warranted to confirm the findings.

3.2 Introduction

Colorectal cancer is one of the leading causes of cancer death in North America (1). The median overall survival of patients with stage IV CRC managed with best supportive care alone is about 5-6 months (2). Systemic therapy provides meaningful improvements in median survival and progression-free survival. Overall, with the judicious use of novel cytotoxic and biologic agents, the median overall survival of patients with stage IV CRC has been extended to approximately two years (3-5).

The optimal surgical management of stage IV CRC that is not amenable to curative resection is unknown. Although administration of systemic therapy in patients with stage IV CRC may convert unresectable into resectable disease, the principal goal of treatment in most patients is to prolong survival, and only about 10-15% patients are alive at five years. Consequently, in patients with stage IV CRC, the potential morbidity of treatment and the treatment's impact on quality of life (QOL) of patients must be considered.

Resection of the primary tumor in patients with stage IV cancer is often performed to deal with presenting primary tumor symptoms and to prevent future primary tumor complications. Potential advantages of resection of the primary tumor are prevention of obstruction and major bleeding, better pain control, and a potential reduction in serious adverse effects such as bleeding and perforation related to novel targeted therapy. Resection may facilitate treatment tolerance (with better response) and potentially improve survival. Conversely, newer-generation chemotherapy in combination with targeted therapy has been associated with response rate of 40-60% (3-5). Systemic therapy not only reduces the size of metastatic lesions, but also shrinks the primary tumor, thereby potentially reducing local complications, such as bowel obstruction, related to primary tumors. Complications after resection of a primary tumor in patients with advanced CRC can delay or prevent initiation of systemic therapy and thereby preclude the associated benefit. Whether primary tumor resection improves disease control by reducing tumor bulk remains unknown.

The available data about the potential benefit of primary tumor resection in patients with stage IV CRC and otherwise unresectable metastatic lesions are limited. Some authors have advocated for surgery (6-8), but other have failed to demonstrate a survival benefit for resection (9-12). Whether

a similar benefit can be achieved in the era of second- and third-generation anticancer agents, which are associated with higher response rates and better overall survival in patients with stage IV CRC, is not known. In spite of uncertain survival benefit, a high rate of surgical resection of the primary tumor has been reported in patients with unresectable metastatic disease (13,14).

We undertook the present comprehensive and critical analysis of the available literature to assess if surgical resection of the primary tumor in patients with advanced colorectal cancer improves outcome.

3.3 Objectives & Outcomes of Interest

3.3.1 Primary Objective

The primary objective was to compare survival in patients with stage IV CRC who did and did not undergo primary tumor resection.

3.3.2 Secondary Objectives

Secondary objectives included determining

- the rates of 30-day postoperative mortality and nonfatal complications in the intervention group.
- the rate of primary tumor complications rate in the control group.
- the rate of non-resection procedures and the QOL in both groups.
- the survival benefit of surgical intervention in the subgroups of patients treated with second- and third-generation anticancer therapy.
- the survival benefit of surgical intervention in the subgroups of minimally symptomatic patients.

3.4 Definitions

All the outcomes of interest were pre-specified and defined. “Primary tumor complications” was defined as development of bleeding, obstruction, and perforation during the study period. “Fatal primary tumor complications” was defined as death within 30 days of bleeding, obstruction and perforation secondary to an intact primary tumor. “Surgical mortality” was defined as death within 30 days of surgery, and “non-fatal surgical complications” was defined as postoperative infection, anastomotic leak, or any other complications recorded 30 days after resection of primary tumor. “Non-resection procedures” included bypass surgery with colostomy formation, endoscopic laser therapy, or placement of endoluminal stents. “Modern chemotherapy” was defined as use of second-generation (irinotecan or oxaliplatin or both) chemotherapy alone or in combination with third-generation agents (bevacizumab or the anti-epidermal growth factor receptor monoclonal antibodies cetuximab or panitumumab). Second-generation chemotherapy became available for clinical use in most centers in the early 2000s. Individual patients data were not available, and so for the purposes of this analysis, all studies that specified the use of second- and third-generation therapy or those that were conducted in whole or in part (≥50%) after the year 1999 were considered studies using second- and third-generation anti-cancer therapy.

3.5 Methods

Our method conformed to the PRISMA statement guidelines (15). Two investigators (SA & RKS) independently evaluated the abstracts, selected relevant articles matching the selection criteria, and independently extracted the data. The Cohen kappa coefficient was used to assess agreement between the two investigators (16). Disagreements between the reviewers were resolved by discussion.

3.5.1 Inclusion and Exclusion Criteria

Studies involving patients with histologically documented adenocarcinoma of colon and rectum and evidence of metastases were included. Only studies with comparative data on the survival of patients with advanced CRC with or without resection of the primary tumor were included. Studies that included data from patients who underwent upfront metastasectomy or from a comparison group of patients with nonsurgical procedures or curative resection were excluded.

3.5.2 Information Sources, Search Strategies and Selection of Studies

An extensive search of reports in the Medline (version 1946 to February 2012), EMBASE (version 1947 to February 2012) and CENTRAL (The Cochrane Central Register of Controlled Trials, The Cochrane Library, Wiley, Issue 3 2012) databases was conducted. Studies were selected using the pre-specified criteria, with restriction to publication dates from 1980 onward, the English language, and studies involving human subjects.

The keywords, synonyms, and controlled vocabulary (MESH & EMTREE) used for the literature search are described in **Appendices A and B**. The computerized literature search was augmented by a manual review of the citations from relevant studies to identify additional article for assessment. The reference lists of all retrieved articles and relevant reviews and clinical practice guidelines were retrieved for identification of additional studies. In case of duplicate publications, the most recent or most complete study was included. A standardized form was used during full-text screening to assess eligibility of studies for inclusion in the present review (**Appendix C**).

3.5.3 Data Collection

The data extracted from the included studies were these: study eligibility, design and characteristics, baseline patients characteristics (age, gender, co-morbid illnesses, Eastern Cooperative Oncology Group performance status, etc.), primary tumor location, disease burden (extent of liver involvement, extra-hepatic disease, etc.), co-interventions (radiation therapy, chemotherapy, second- and third-generation chemotherapy, metastasectomy rate, etc.), and primary and secondary outcomes (median overall survival, two-year survival, 30-day post-operative mortality, primary tumor complications and nonsurgical procedures, and QOL). Attempts were made to contact the corresponding authors of all the eligible studies for relevant missing information (**Appendices D & E**).

3.5.4 Validity Assessment

Study designs were evaluated according to whether they were retrospective or prospective, and randomized or observational. Two authors independently evaluated all the included studies using a list of selected quality items assessing components of validity and bias. Disagreements were resolved by discussion. Risk of bias in the eligible studies was assessed by each reviewer using guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (17). For observational studies "the Newcastle-Ottawa Quality Assessment Scale" was applied [18]. The Newcastle-Ottawa Scale consists of nine items grouped into three sections that are relevant to the quality of an observational study (**Appendix F)**.

For each outcome of interest, validity scores were evaluated as follows: ≤ 5: low quality; 6-7 medium quality; 8-9 high quality (18). The Cohen kappa coefficient was used to assess agreement between the two investigators with respect to the outcomes of interest (16).

3.5.5 Analysis & Synthesis of Result

Results of the included studies for primary outcome were combined in a formal meta-analysis to produce an overall estimate of surgical intervention. For quantitative pooling, the DerSimonian and Laird random-effects model was used, and all calculations were performed using the Review Manager analysis software (RevMan, version 5.1.2: The Cochrane Collaboration, http://ims.cochrane.org/revman). Treatment effects are expressed as hazard ratios (HR) with corresponding 95% confidence intervals (CI). For studies that did not provide numeric information about time to event, the HR and variance were estimated using Kaplan-Meier survival curves (19). A P-value of 0.05 was used as the cut-off value for statistical significance. Funnel plots were constructed to evaluate potential publication bias. Heterogeneity across studies was assessed using a statistical test, with the proportion of variation being expressed as I^2. All other outcomes are presented descriptively, and results are presented as mean or median of variables in the analyzed studies. Single-group analyses were done for surgical mortality and complication rates (intervention group) and primary tumor complication rate (control), because those outcomes were not applicable to both groups. A sensitivity analysis was performed if appropriate.

Pre-specified subgroup analyses were performed to assess the survival of patients with minimally symptomatic primary tumor and of patients involved in studies that offered treatment with second- and third-generation anticancer therapy. Risk of bias for all outcomes was assessed across the analyzed studies in duplicate by two reviewers and reported using the GRADE scale (20).

3.6 Results

3.6.1 Study Selection

Figure 3.1 shows the flow chart of the search procedure, which identified 3379 citations. Publications not meeting the inclusion criteria and duplicate publications were excluded after a review of titles and abstracts. Thirty-seven potentially eligible articles underwent full-text assessment to determine their eligibility for inclusion in the final analysis. Fifteen studies (reported

in fourteen articles) were identified as meeting the eligibility criteria (6-12,21-26). Kappa agreement scores between the two abstractors with respect to "screening for the citations" and "full text screening" were 0.68 and 0.86 respectively, suggesting substantial-to-excellent agreement.

Of twenty-three full-text articles that were excluded, twelve had no comparator nonsurgical group (27-38); four used a non-resection group (that is, ostomy procedures) as comparators (39-42); and another four used patients who underwent curative surgery as the comparator group (43-46). Two studies, each with four comparator groups, provided minimal information about those groups, and one had a patients population that overlapped with the population of another study included in the present review (14,47). One study whose non-resection group contained fewer than five patients was excluded after discussion between the reviewers (48). The asymmetry of the funnel plot around the point estimate suggests an element of publication bias (**Figure 3.2**)

3.6.2 Study Characteristics & Risk of Bias

Table 3.1 describes the characteristics and risk of bias of the included studies. As anticipated, no prospective trial describing randomization between surgical and nonsurgical treatment was found. The study by Venderbosch et al. was a retrospective analysis of two randomized studies reported by Koopman et al. and Tol et al. (CAIRO and CAIRO I) [7,49,50]. Eight studies originated in Europe; five, in North American; and one, in Asia. Six studies exclusively involved minimally symptomatic patients, and ten studies met the pre-specified criteria for use of modern anticancer therapy. All but one study imposed no age restriction (13).

All included publications reported retrospective observational studies. Using validity scoring for observational study, no study met the criteria for good quality study for any outcome of interest. For the primary outcome overall survival, nine of fifteen studies were of low quality, and the remaining six were of fair quality (**Appendix N**).

With respect to secondary outcomes, the quality of evidence was lower overall than it had been for the primary outcome. Reporting bias was noted for all the secondary outcomes: six studies did not report postoperative mortality rate (7-10,22); eight studies did not provide data for post-operative complications or morbidity (7,8,10,13,22,23,25); four lacked information about the rate of primary tumor complications (7,21,22); six provided no information on non-resection procedures (6,7,9,24,25); and no study provided information about QOL.

3.6.3 Patients Characteristics

The included studies involved a total of 12,456 patients, among whom 8620 (69%) underwent surgery as initial treatment, and 3796 (31%) were initially received systemic therapy. Several studies did not provide information about the baseline characteristics of the patients. All except one study provided information about systemic therapy (9); eight studies provided information about performance status (7,8,10,11,22,25,26); and only four studies provided information about comorbid illnesses (6,8,13,25). **Table 3.2** describes the baseline characteristics of the patients in the analyzed studies. Median age was 61 years (range: 19-96), and 41% (95% CI: 36.8-45.1) were women. Of the patients overall, 16.6% (95% CI: 7.9-25.2) had an ECOG performance status greater than 1, and 54% (95% CI: 40-69) patients had more than 25% liver involvement. The

tumor was located in the rectum in 26% (95% CI: 19.7-32.2) of the patients: 21.9% (95% CI: 14.3-29.5) in the resection group, and 31% (95% CI: 22.8-39.2) in the control group. With respect to systemic therapy, 82% (95% CI: 73-92) patients received chemotherapy, and 64% (95%CI: 35-84) received second- and third-generation therapy. Only in CAIRO and CAIRO II trials, patients in both groups uniformly received second-generation and third-generation therapy, respectively (49,50). The mean rate of metastasectomy was 11.4% (95% CI: 3.5-19.3) in the intervention group and 9.3% (95% CI: 0-18.2) in the control group.

3.6.4 Overall Survival

Table 3.1 describes survival and secondary outcomes for the individual studies, and **Table 3.3** describes summary findings and risk of bias for the studies overall. Median survival was 15.2 months (range: 10-30.7) in the resection group and 11.4 months (range: 3-22) in the non-resection group. A quantitative meta-analysis using the data of all fifteen studies revealed that, compared with no surgery, primary tumor resection was associated with a significant improvement in survival (HR: 0.69; 95% CI: 0.61-0.79; P<0.00001; **Figure 3.3**). Subgroups analyses were performed for more homogenous patient population with respect to symptoms and type of systemic therapy (see the Subgroup Analyses section).

3.6.5 Sensitivity Analysis

Only seven studies reported HRs and 95% CI; for the remaining 8 studies, we used the method suggested by Tierney et al. to estimate HRs and variances (19). In a sensitivity analysis pooling the data of seven studies (7,8,10,11,24,26), the HR for survival was 0.52 (95% CI: 0.40-0.68) favoring the resection group (**Figure 3.4**). Among fifteen studies reviewed, the study by Temple et al. was conducted in patients more than 65 years of age. A sensitivity analysis that excluded the Temple et al. study revealed a HR for survival of 0.68 (95% CI: 0.57-0.80; **Figure 3.5**).

3.6.6 Secondary End Points

The surgical mortality rate was reported in nine studies. The mean 30-day postoperative mortality rate was 4.9% (95% CI: 0-9.7%) in the intervention group. Only seven studies reported nonfatal surgical complications, including anastomic leaks, wound infection, and other complications. The mean surgical morbidity rate was 25.9% (95% CI: 20.1-31.6). Most studies did not separate major and minor complications. The mean rate of anastomotic leak, a serious postoperative complication, was 3.2% (95% CI: 0-8.3).

The mean rates of primary tumor complications and intestinal obstruction secondary to the primary tumor were 29.7% (95%CI: 18.5-41.0) and 23.4% (95% CI: 14.1-32.7) respectively. Most studies failed to specify major and minor bleeding. No study specifically reported the rate of fatal primary tumor complications. The non-resection surgical procedures rate in the control group was 27.6% (95% CI: 15.4-39.9). Only three studies reported rates of non-resection surgical procedures in the intervention group, for whom the rate was 4.2 (95% CI: 0-10.1). Because all studies were retrospective, none assessed QOL.

3.6.7 Sub-Groups Analyses

Table 3.4 presents information about various outcomes in the patient subgroups of interest.

3.6.7.1 Studies Using Second- and Third-Generation Anti-Cancer Therapy

In the subgroup of patients receiving modern chemotherapy, median overall survival in the group undergoing surgery was 18.7 months (range: 11-30.7); it was 12.85 months (range: 5.8-22) in the control group. The HR for survival in this subgroup was 0.68 (95% CI: 0.56-0.83) compared with a HR of 0.73 (95% CI: 0.59-0.90) in patients treated with an older regimen, which favors surgical intervention (**Figure 3.6**). A test for interaction between the groups was non-significant. The mean 30-day postoperative mortality rate in the group treated with modern chemotherapy was 3.9% (95% CI: 0-11). The mean rates of primary tumor complications and non-resection procedure in the control group were 27.4% (95% CI: 16.4-38.5) and 27% (95% CI: 12.5-41.6).

3.6.7.2 Studies with Minimally Symptomatic Patients

The median overall survival in the resection group was 18.5 months (range: 14.5-23); it was 13.15 months (range: 5.8-22) in the control group. The HR for survival in minimally symptomatic patients was 0.67 (95% CI: 0.48-0.94; **Figure 3.7**) compared with a HR of 0.75 (95% CI: 0.67-0.84) in symptomatic patients (test for subgroups interaction, p=0.53), which favors the intervention group.

In minimally symptomatic patients, the mean 30-day post-operative mortality rate was 1.6% (95% CI: 0-74.8), with four of six studies reported 0% surgical mortality. The mean rates of primary tumor complication and non-resection procedures in the control group were 25.6% (95% CI: 5.9-45.2) and 22.2% (95% CI: 0-49.1)

3.7 Discussion

Our review demonstrates a consistent trend favoring noncurative surgical management of primary tumors in patients with stage IV CRC. Overall, the group treated with surgery experienced a 31% relative improvement in survival, with an absolute survival difference of approximately 4 months. A survival benefit of similar magnitude was demonstrated in the other reviews (51,52); however, a recent review did not support the surgical intervention (53). We found comparable survival benefit in studies using newer-generation chemotherapies and in minimally symptomatic patients. Notably, the pooled estimate for survival revealed considerable heterogeneity across the studies. Conceivably, those studies involved clinically heterogeneous groups with respect to patient population (age, performance status, co-morbid illnesses, disease burden, primary tumor related symptoms, for example) and co-intervention (type of systemic therapy, differing rate of metastasectomy). Likewise, considerable variability was noted across the different studies designs, and the risk of bias was suggestive of methodological diversity. Despite those limitations, we opted to report the pool result, because the direction of effect was consistent across the studies and subgroups albeit of varying different magnitude.
Of special interest, a quantitative analysis excluding low-quality studies revealed a HR for survival of 0.64 (95% CI: 0.45-0.92) favoring surgical intervention (**Figure 3.8**). Because of selective

reporting and a lack of explicit information in some studies, examination of heterogeneity with respect to important clinical variables (with the exception of underlying symptoms and type of treatment) was not feasible. Notably, test for heterogeneity was no longer significant after exclusion from the pool of three studies that had either larger effect size or a very narrow confidence interval, suggesting statistical heterogeneity (**Figure 3.9**)[11,13,24]. Likewise, in the subgroup analysis, the test for heterogeneity was nonsignificant after exclusion of study by Glazia et al. Because of the concern of publication bias, overestimation of the intervention effect relative to the true outcome is quite plausible.

A high rate of postoperative complications can offset the survival benefit associated with surgery. Our review was limited by selective reporting of surgical mortality and morbidity across the included studies. Compared with patients having localized disease, those with advanced CRC tended to experience increased mortality after resection of the primary tumor. Although four of nine studies reported no postoperative mortality, the rate in some studies was not trivial, reaching up to 16%. As anticipated, a higher mortality rate has been associated with emergency surgery (21,23). Fewer than half of the included studies reported nonfatal operative complications, and many failed to distinguish between major and minor complications, limiting the clinical relevance of the information.

The mean rate of primary tumor complications was 27%, but reached as high as 63%. Complication rates of more than 50% were noted mostly in older studies. Realistically, there is no evidence to suggest that response rates for the primary tumor are inferior to those for metastases. Three retrospective studies specifically investigated the risk of primary tumor complications in patients with non-resection management and reported complications rates between 3 and 17% (54-56).

When anti-vascular endothelial growth factor therapy is combined with cytotoxic agents in patients with an intact primary tumor, a concern about perforation risk arises (57). Two recent uncontrolled prospective studies did not support prophylactic resection of the primary tumor in minimally symptomatic patients treated with targeted therapy (58,59). In one cohort of 233 patients with intact primary tumor, only 7% of patients required emergency palliative surgery (58). Use of bevacizumab, primary tumor location, and metastatic disease burden were not associated with an increased intervention rate. The other phase II trial, which used an oxaliplatin and bevacizumab combination regimen, reported a 14% major complications rate related to the intact primary tumor (59). Median overall survival of the treated cohort was 19.9 months. The author concluded that survival is not compromised by leaving the primary colon tumor intact. The mean non-resection procedure rate was 28% in patients with an intact primary tumor, which accorded with the primary tumor complications rate of 30% reported by McCahill et al. (59). Only three studies reported non-resection procedures in the intervention group, and as expected the numbers were much lower than those in the control group.

Quality of life is an important outcome that helps patients and their physicians choose appropriate treatment. No study in our review reported QOL. Because major intestinal complications such as obstruction, perforation, and hemorrhage related to the primary tumor, and postoperative complications are likely to be associated with a significant adverse effect on QOL, QOL can be indirectly assessed by reviewing the rates of surgical and primary tumor complications. A surgical

intervention with a low complication rate could potentially result in a favorable QOL as a result of fewer non-resection interventions, lack of primary tumor related complications, and better tolerance for systemic therapy.

Potential limitations of the present review are the substantial number of low-quality studies, publications bias, and selective reporting. Importantly, all outcomes in the review were evaluated retrospectively, and patients were not randomized to surgery or non-surgical management. Several studies did not provide baseline prognostic characteristics for their groups, and others showed significant imbalance in baseline characteristics. Furthermore, few studies provided detail information about the use and type of systemic therapy in each group, making it difficult to assess the relative contribution of resection to outcomes. Those concerns affect the validity of the survival benefit observed in our review, which may simply reflect the selection of younger and healthier patients with good performance status and low disease burden for surgery.

3.8 Conclusions

The retrospective data favor resection of the primary tumors in patients with advanced CRC. However, the very low quality of the current evidence requires that good-quality cohort studies and adequately powered, well designed randomized trials be conducted to assess all the important outcomes in this patient population. We have begun a large population-based cohort study in the province of Saskatchewan, and European investigators are currently working on several randomized trials, including CAIRO 4, to resolve this matter.

3.9 References

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Table 3.1: Study characteristics: Design, quality, population, interventions and outcomes of interest.

Study & year of publication	Study Design	Duration of study & Country	N	Quality*	Patients	Co-interventions	Outcomes
Aslam et al, 2010[21]	Retrospective multi-centers observational study	1998-2007; UK	T: 647 I: 366 C: 281	low 5/9	minimally symptomatic	chemotherapy I: 63%, C: 36%†	median OS 14.5 (I) vs. 5.8 (c) months (p<0.05); POMRI 7%; POCRI 32%; NRPC 46%
Benoist et al, 2005[12]	Retrospective single institutional case-control study	1997-2002; France	T: 59 I: 32 C: 27	fair 6/9	asymptomatic or minimally symptomatic	chemo & novel therapy I: 94%, C: 100%; metastasectomy I: 16%, C: 22%	median OS 22 (I) vs. 23 (c) months (p=NS); POMRI 0%; POCRI 22%; PTCRC 15%; NRPC 15%
Chan et al, 2010[22]	Retrospective population based study	2000-2002; Canada	T: 411 I: 286 C: 125	low 5/9	symptomatic & asymptomatic	chemotherapy I: 61%, C: 58%; novel therapy I: 57%, C: 36%; metastasectomy I: 10%, C: 0%	median OS 14 (1) vs. 6 (c) months (p=<0.05); NRPC 22%; NRPI 4%
Evans et al, 2009[23]	Retrospective single institutional observational study	1999-2006; UK	T: 97 I: 45 C: 52	low 4/9	symptomatic & asymptomatic	chemotherapy I: NP, C: 42%†; radiation therapy I: NP, C: 8%	median OS 11 (I) vs. 7 (c) months (p=NS), POMRI 16%; PTCRC 23%; NRPC 50%
Galizia G et al, 2008[11]	Retrospective single institutional observational study	1995-2005; Italy	T: 65 I: 42 C: 23	fair 6/9	asymptomatic or minimally symptomatic	chemotherapy I: 100%, C: 100%†; metastasectomy I: 12%, C: 4%	Median OS 15.2 (I) vs. 12.3 (c) months (p=0.003); POMRI 0%; POCRI 21% PTCRC 31%; NRPC 22%

Karoui M et al, 2011[8]	Retrospective multi-centers observational study	1998-2007; France	T: 208 I: 123 C: 85	low 5/9	symptomatic & asymptomatic	chemotherapy I: 100%, C: 99%; novel therapy I: 89%, C: 93%; metastasectomy I: 23%, C: 29%	Median OS 30.7 (I) vs. 21.9 (c) months (p=0.004); PTCRC 27%; NRPC 27%
Konyalian VR et al, 2007[24]	Retrospective single institutional cohort study	1991-2002; USA	T: 109 I: 62 C: 47	low 5/9	symptomatic & asymptomatic	chemotherapy† I: 71%,C: 60%; radiation therapy I: 27%, C: 34%	Median OS 12.5 (I) vs. 4.6 (c) months (p<0.05); POMRI 5%; POCRI 20% PTCRC 57%
Michel P et al, 2004[25]	Retrospective single institutional observational study	1996-1999; France	T: 54 I: 31 C: 23	low 4/9	asymptomatic or minimally symptomatic	chemotherapy I: 97%,C: 100%; novel therapy I: 80%, C: 83%; metastasectomy I: NP, C: 9%	Median OS 21 (I) vs. 14 (c) months (p=NS); POMRI 0%; PTCRC 35%
Ruo L et al, 2003[6]	Single institutional retrospective observational study	1996-1999; USA	T: 230 I: 127 C: 130	low 4/9	asymptomatic or minimally symptomatic	chemotherapy † I: NP,C: 83%	Median OS 16 (I) vs. 9 (C) months (p=<0.05); POMRI 2%; POCRI 21%; PTCRC 29%
Scoggins CR et al,1999[9]	Single institutional retrospective observational study	1985-1997; USA	T:89 I:66 C:23	low 4/9	Symptomatic & asymptomatic	No information was provided about other interventions	Median OS 14.5 (I) vs. 16.6 (c) months (p=NS); POCRI 30%; PTCRC 9%
Seo JG et al 2010[26]	Single institutional retrospective observational study	2001-2008; South Korea	T:277 I:144 C:83	fair 6/9	asymptomatic or minimally symptomatic	chemotherapy I: 100%, C: 100%; novel therapy I: 85%, C: 82%; radiation therapy I: 10%, C: 12%	Median OS 22 (I) vs. 14 (c) months (p=NS); POMRI 0%; POCRI 35%; PTCRC 19%; NRPC 7%; NRPI 2%

Tebutt NC et al, 2003[10]	Single institutional retrospective observational study	1990-2000; UK	T:362 I:208 C:82	low 5/9	symptomatic & asymptomatic	Chemotherapy I: 100%, C:100%; novel therapy 0%; radiation therapy I: 10%, C: 18%; mestatasectomy I: 2%, C: 1%	Median OS 14 (I) vs. 8.2 (c) months (p=NS); PTCRC 19%; NRPC 6.7%; NRPI 9.7%
Temple et al, 2004[13]	Population based study using SEERS & Medicare data	1991-99; USA	T:9011 I:6464 C:2542	fair 6/9	65 yrs or older symptomatic & asymptomatic	chemotherapy I: 47%, C: 31%; radiation I: 12%, 15%; metastasectomy I: 5.2%, C: 1.3%	Median OS 10 (I) vs. 3 (c) months (p<0.05); POMRI 9%; PTCR 63%, NRPC 32%
Venderbosch et al, 2011 (CAIRO)[7,49]	Retrospective multi-centers cohort of a RCT*	2003-2004 (recruited period); Netherland	T:399 I:258 C:141	fair 6/9	Symptomatic & asymptomatic	100% novel therapy in both groups	Median OS 16.7 (I) vs. 11.4 (c) months
Venderbosch et al, 2011 (CAIRO 2)[7,50]	Retrospective multi-centers cohort of a RCT*	2005-2006 (recruited period); Netherland	T:488 I:289 C:159	fair 6/9	Symptomatic & asymptomatic	100% novel therapy in both groups	Median OS 20.7 (I) vs. 13.4 (c)months

C=control group; I=intervention group; N=number; NP=not provided; NS=not significant; OS= overall survival; POMRI=Post-operative mortality rate intervention group; POCRI=Post-operative non-fatal complication rate intervention group; PTCRC= Primary tumor complication rate in control group; NRPC=Non resection procedures in control group; NRPI=Non resection procedures in intervention group; T=total; UK= The United Kingdom; USA= The United States of America *studies methodological quality was assessed by using Ottawa-Newcastle scale for non-randomized study, please see the text for score detail; †Information about novel therapy (2nd and 3rd generation anti-cancer therapy) was not provided. 6 studies did not report post-operative mortality; 8 studies did not provide post-operative morbidity; 4 studies did not provide information on primary tumor complication rates; 6 studies did not provide any information on non-resection procedures in the control group and 12 studies did not provide information in the intervention group; no study provided information about quality of life.

Table 3.2: Baseline characteristics of the patients in the control and intervention groups.

Patient Characteristics	Totals N=12456 Mean % (95% CI)	Control group N=3796 (30.4%) Mean % (95% CI)	Intervention group N=8620 (69.6%) Mean % (95% CI)
Median Age (range)	61 yrs (19-96)	63 yrs (19-96)	60 yrs (22-92)
Female*	41 (36.8-45.1)	38.7 (31.3-46.2)	43.5 (38.5-49.0)
Rectal Tumor **	26 (19.7-32.2)	31 (22.8-39.2)	21.9 (14.3-29.5)
ECOG PS† >1	16.6 (7.9-25.2)	18.1 (2.5-33.7)	15 (3.0-27)
>25% liver involvement‡	54 (40-69)	54.7 (25.6-83.7)	54.2 (34.4-73.9)
Peritoneal disease¥	21.6 (13.3-30)	22 (2.3-41.7)	21.4 (6.5-36.3)
Received RadiationЂ	16.2 (9.5-23.0)	17.4 (5.0-29.8)	14.8 (1.7-27.8)
Received Chemotherapy††	82 (73-92)	79.2 (63.3-95.1)	86.1 (73.6-98.6)
Single agent fluoropyrimidine‡‡	88.6 (80-97.1)	88.1 (73.6-100)	89.0 (76.2-100)
2^{nd} or 3^{rd} generation therapy‡‡	64 (35-84)	66 (33.4-98.6)	67.2 (36.3-98.2)
Underwent metastasectomy€	10.3 (4.6-16.1)	9.3 (0-18.2)	11.4 (3.5-19.3)

ECOG= Eastern Oncology Cooperative Group Performance Status , *two studies did not provide gender distribution data[9,23]; ** two studies did not provide information about location of primary tumor[23,24]; †seven studies did not provide information about PS[6,9,12,13,21,23,24]; ‡ six studies provided information about extent of liver involvement[6,11,12,21,25,26]; ¥ Five studies provided information about peritoneal disease[8,10,21,25,26]; Ђ Five studies provided data reading palliative radiation[10,13,23,24,26]; ††one study did not provide information about chemotherapy[9]; ‡‡six studies did not provide information[6,11,13,21,23,24]; € seven studies provided information[8,0,11-13,22,25].

Table 3.3: Evidence profile and summary of primary and secondary outcomes.

Outcomes	Number (studies)	Control Group (range)	Intervention Group (range)	Quality of Evidence GRADE [20]	Comments
Median overall survival in months (range)	12,456 (15 studies)	11.4 (3-22)	15.2 (10-30.7)	very low	HR for survival 0.69 (95% CI: 0.61-0.79) favoring the intervention group. Significant imbalance in patients characteristics; most studies did not provide information on performance status and co-morbid illnesses
Quality of life (QOL)	0	See comments	see comments	NA	All studies were retrospective & QOL was not measured in any study
Mean Surgical mortality rate % (95% CI)	10,499 (9 studies)	NA	4.9 (0-9.7)	low	4 studies reported 0 post-operative mortality, mortality rate of >5% was noted in the older studies
Mean Surgical morbidity rate (95% CI)	1,426 (7 studies)	NA	25.9 (20.1-31.6)	very low	For post-operative complications most studies did not distinguish between major and minor complications
Primary tumor complications rate % (95% CI)	10,511 (11 studies)	29.7 (18.5-41.0)	NA	very low	6 of 12 studies had both symptomatic & asymptomatic patients
Mean non-surgical procedure rate % (95%CI)*	10,725 (9 studies)	27.6 (15.4-39.9)	4.2 (0-10.1) See comments	very low	Only 3 studies (n=862) provided non-resection procedure rate in the intervention group

NA=not applicable; *Non-surgical procedures include bypass surgery and placement of stent

Table 3.4: Primary and secondary outcomes in subgroups of patients with respect to patients population and interventions.

Subgroups	Mean Survival months (95% CI)	Hazard Ratio for survival (95% CI)	Post-operative mortality % (95% CI) I	Non-fatal post-operative complicati-ons % (95% CI) I	Primary tumor complicati-ons % (95% CI) C	Non-surgical procedure % (95% CI) C	QOL Ђ
Asymptomatic or minimally symptomatic patients							
Intervention	18.6 (14.6-22.6)	0.67 (0.48-0.94)‡	1.6 (0-4.8)	25.6 (5.9-45.2)	NA	2*	
Control	12.8 (7.1-18.6)	0.78 (0.72-0.84)†	NA	NA	25 (15.3-36.1)	22.2 (0-49.1)	
Symptomatic and asymptomatic patients							
Intervention	16.0 (11.1-20.9)	0.75 (0.67-0.84)‡‡	10 (0-23.8)	25 (12.6-37.4)	NA	5.3 (2-8.7)	
Control	10.0 (5.1-14.9)	0.79 (0.70-0.90)††	NA	NA	27 (7.5-46.5)	32.8 (13.3-52.2)	
Studies with 2nd & 3rd generation therapy							
Intervention	18.9 (14.8-23.0)	0.68 (0.56-0.83)ђ	3.9 (0-11)	27.4 (16.4-38.5)	NA	3 (0-5.5)	
Control	12.8 (8.6-17.0)	0.75 (0.67-84)Ђ	NA	NA	25 (17-33)	27 (12.5-41.6)	
Studies with 1st generation therapy							
Intervention	13.4 (10.6-16.2)	0.73 (0.59-0.90)ђђ	5.3 (0-14.1)	23.7 (10-37.4)	28.2 (2.5-53.9)	6.7**	
Control	8.1 (1.7-14.8)	0.81 (0.72-0.92)ЂЂ	NA	NA	NA	32**	

I: intervention group, C: control group, QOL: quality of life; NA=not applicable. Ђ non study report QOL; * only 1 of 6 studies reported non-resection surgical procedure in the intervention group; *only one of 5 studies reported non-resection procedure in the intervention group & control group; ‡ test for heterogeneity was significant for data using 6 studies, †test for heterogeneity was not significant after excluding the data from study by Galizia et al[11]; ‡‡ test for heterogeneity was significant for data using 9 studies, †† test for heterogeneity was not significant after excluding the data from studies by Konyalian et al[24], Temple et al[13], and CAIRO[7]; ђ test for heterogeneity was significant for data using 10 studies, Ђ test for heterogeneity was not significant after excluding the data from study by Aslam et al[21],Galizia et al[11]; ђђ test for heterogeneity was significant for data using 5 studies, ЂЂ test for heterogeneity is not significant after excluding the data from study by Konyalian et al[24].

Figure 3.1: Flow of information through the different phases of literature search.

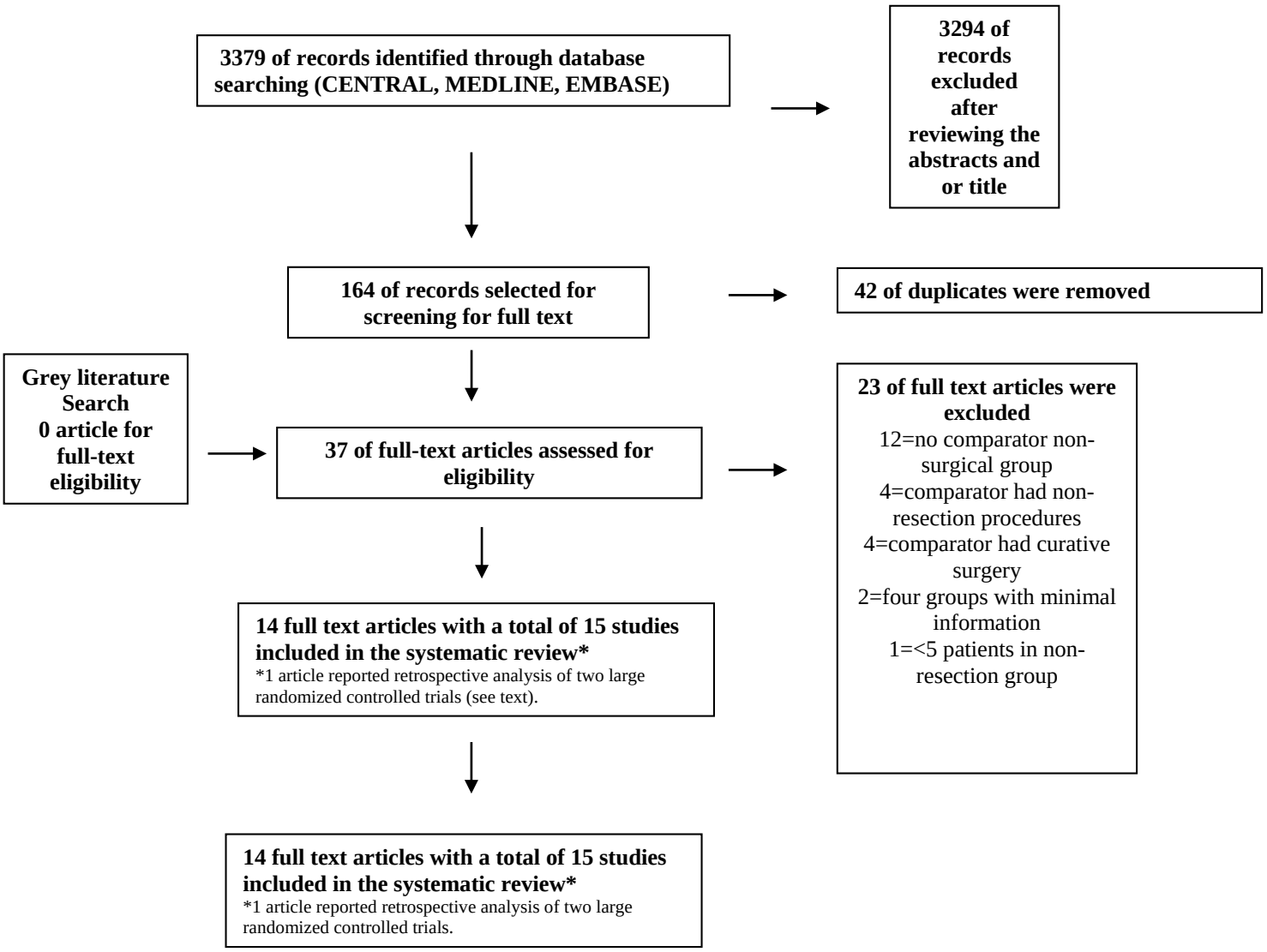


Figure 3.2: Funnel plot shows asymmetry of studies around the point estimate, suggestive of publication bias.

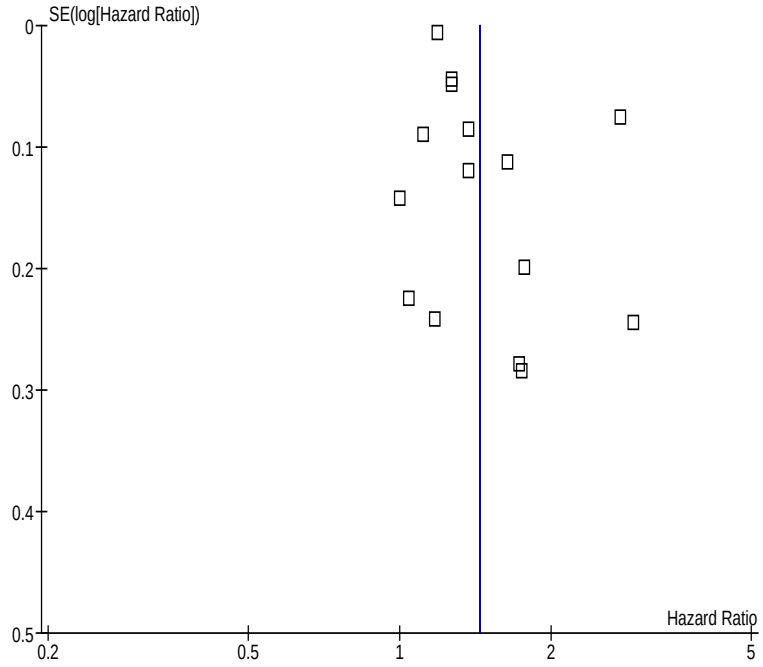


Figure 3.3: Hazard ratio with 95% confidence interval for overall survival, all reviewed studies, favors the intervention group.

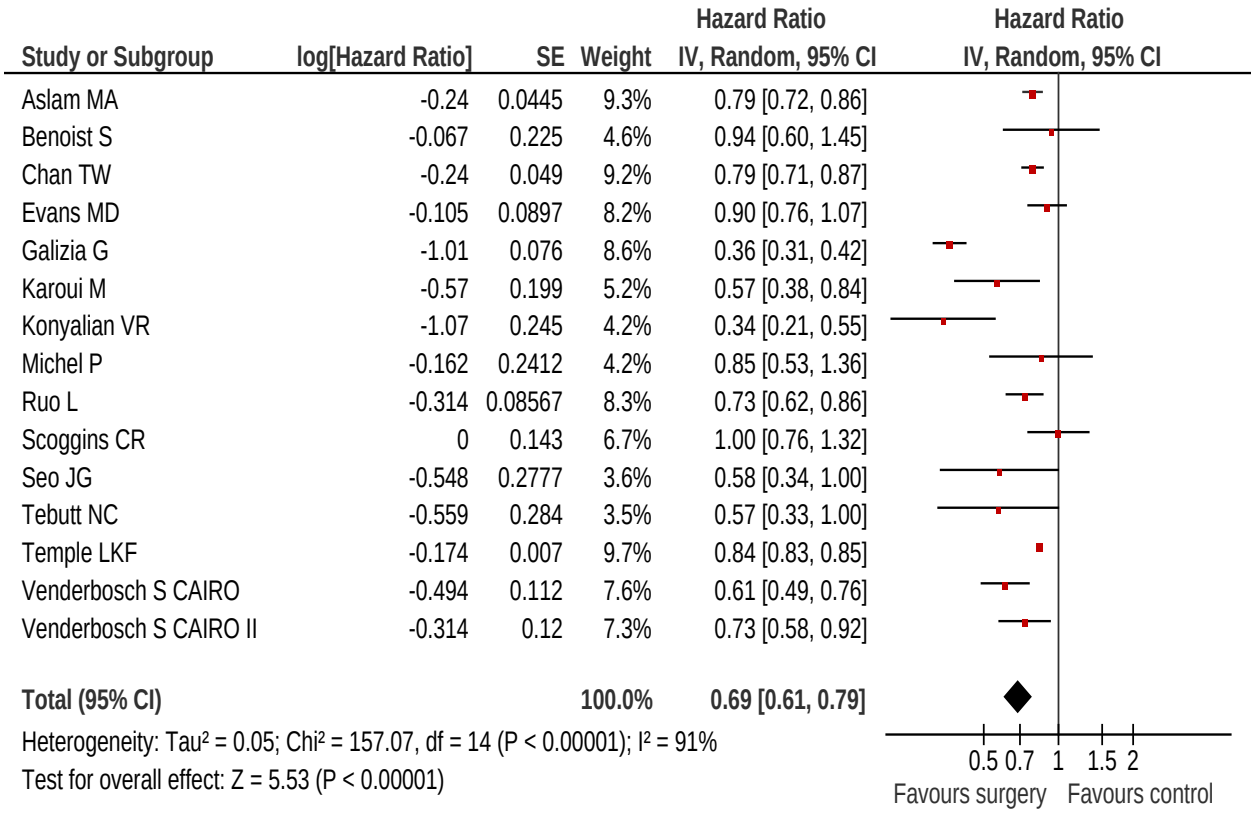


Figure 3.4: Sensitivty analysis of overall survival for seven studies reported a hazard ratio favoring the intervention group.

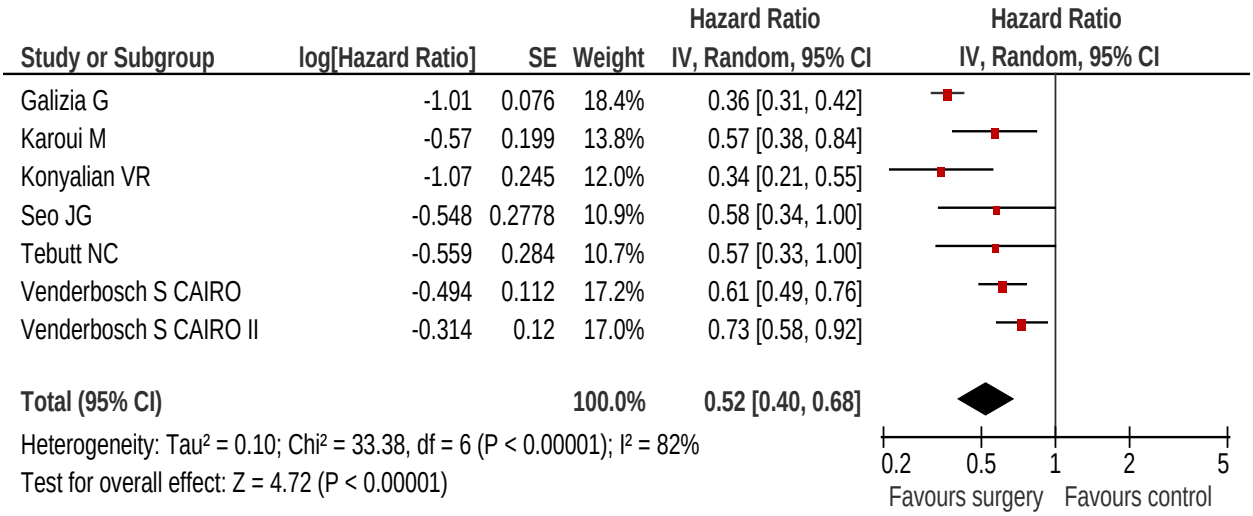


Figure 3.5: Sensitivity analysis of overall survival, excluding the stuy by Temple et al. favors the intervention group.

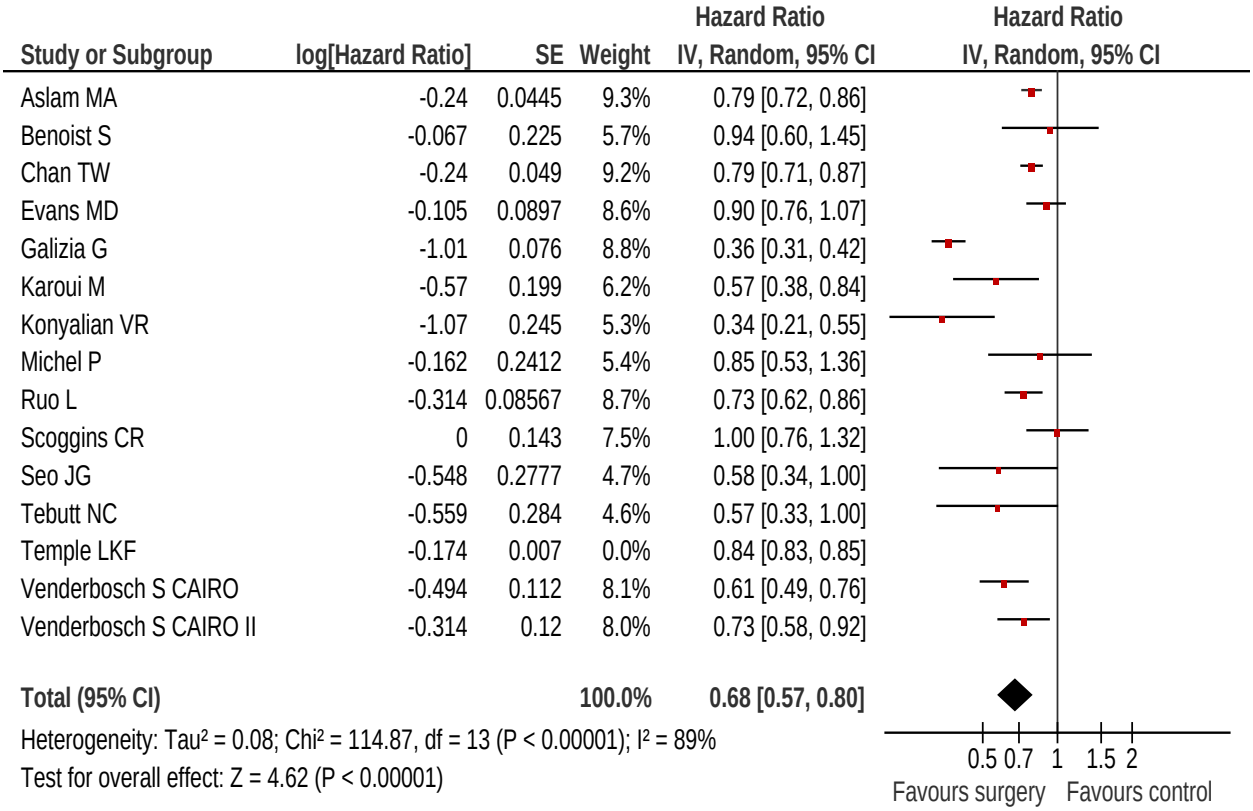


Figure 3.6: Hazard ratio with 95% confidence interval for overall survival, subgroups based on type of chemotherapy.

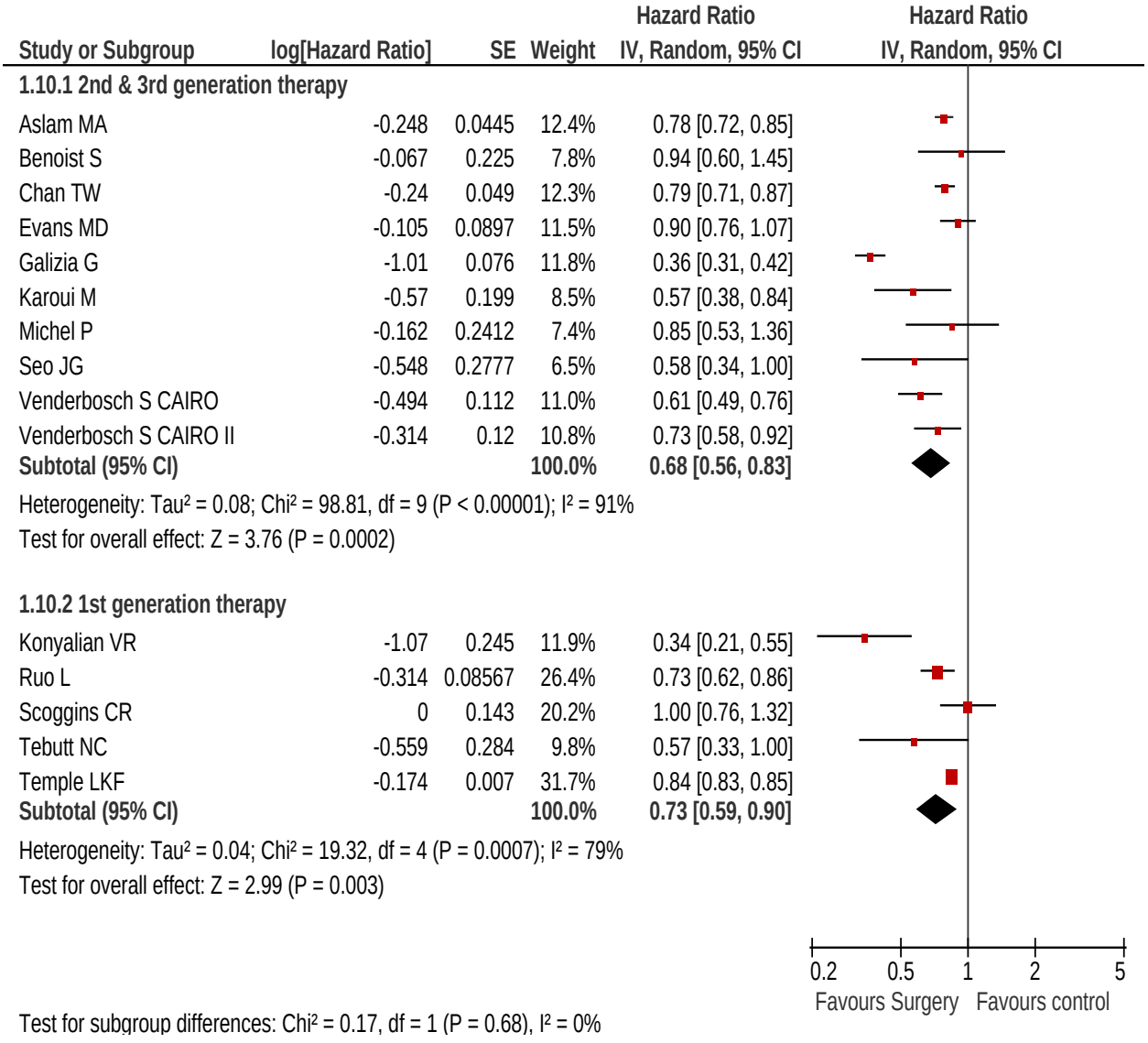


Figure 3.7: Hazrad ratio with 95% confidence interval for overall survival, subgroups based on extent of the symptoms.

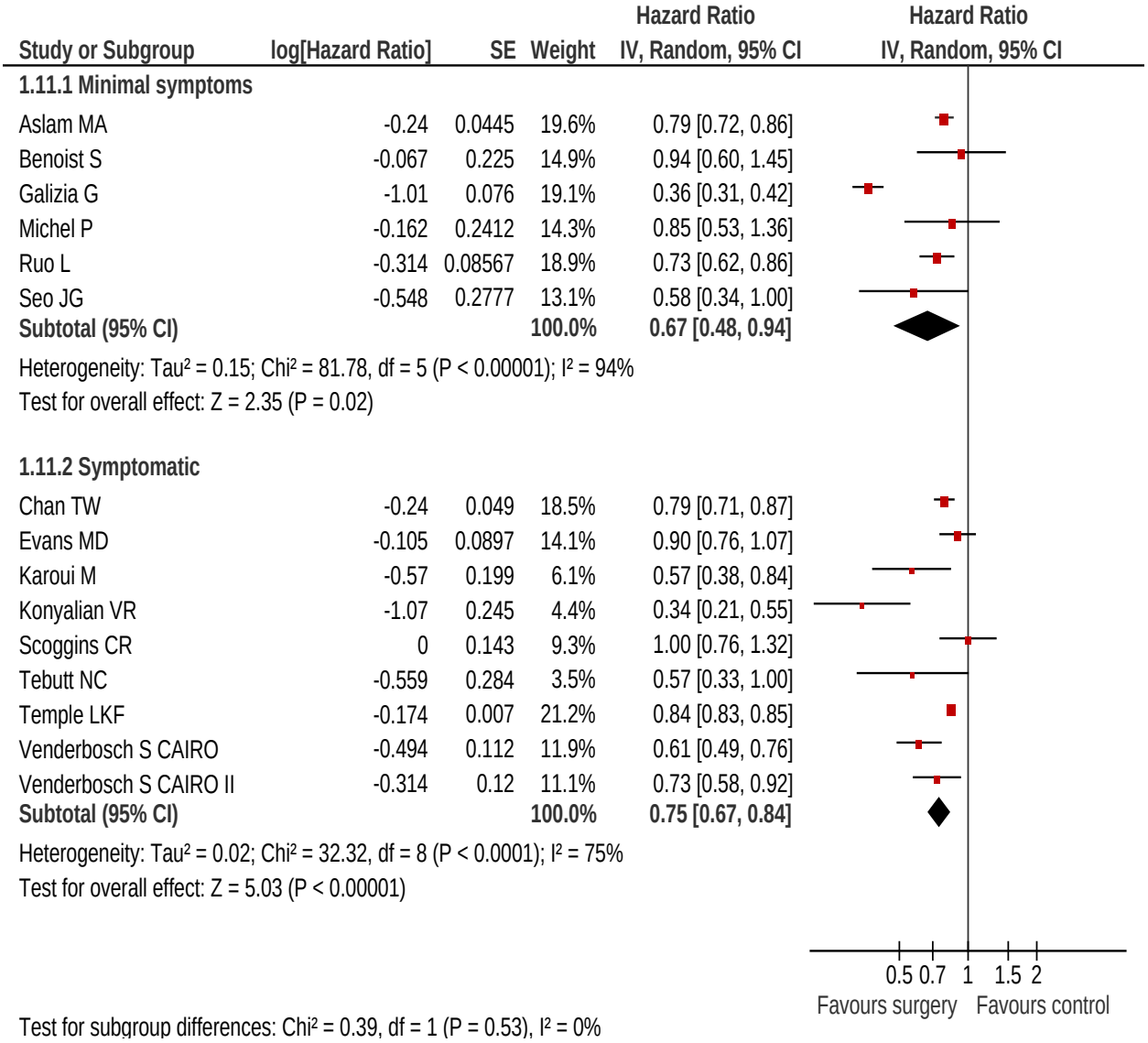


Figure 3.8: Hazrad ratio with 95% confidence interval for overall survival in the subgroups, based on a score of "fair" on Ottawa-Newcastle Score.

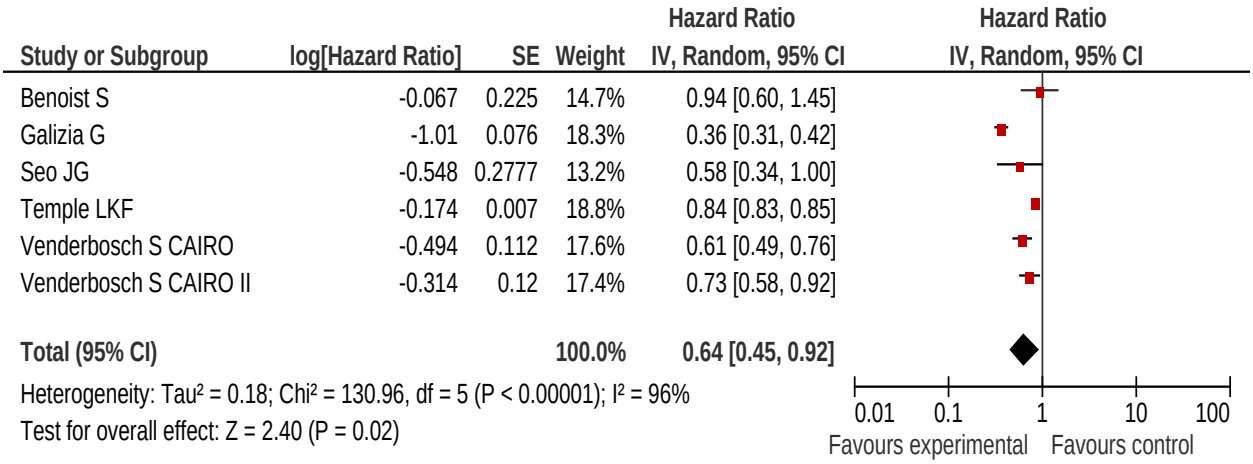
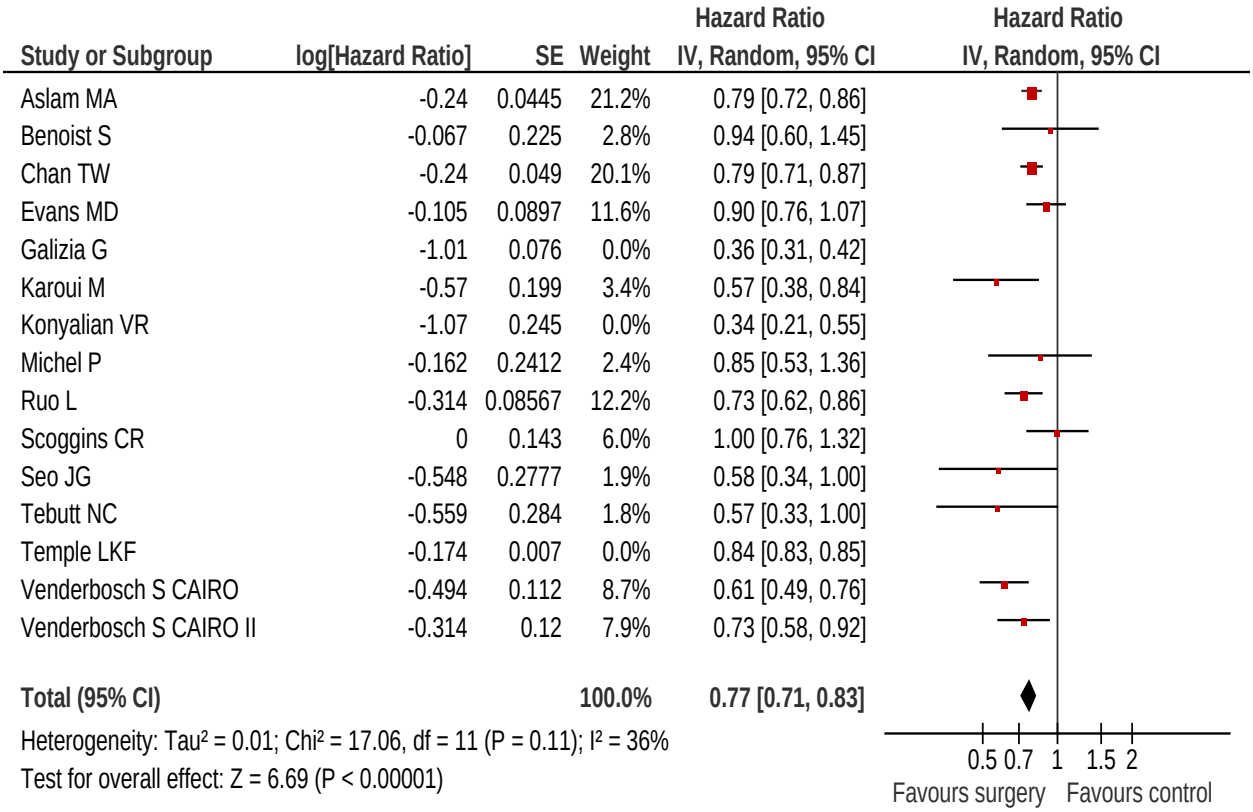


Figure 3.9: Hazrad ratio with 95% confidence interval for overall survival, twelve studies (excluding three with a large effect size or narrow confifedence interval), favors the intervention group with low heterogeneity.



CHAPTER 4 – COHORT STUDY (1992-2005): PRIMARY TUMOR RESECTION IN METASTATIC COLORECTAL CANCER

Although the retrospective data favors primary tumor resection in patients with stage IV CRC, many studies failed to provide baseline characteristics of patients in both groups. Others studies showed significant differences between the two groups and failed to control for the differences. Hence, validity of survival benefit observed in these studies has been questioned and is believed to be biased by the selection of healthier and younger patients for surgery. The current very low quality evidence necessitates the future need of good quality cohort studies and well-designed randomized trials assessing important outcomes. In the absence of randomized controlled trial, we undertook this study to investigate the optimal management of primary tumor in patients diagnosed with stage IV CRC cancer.

This chapter addresses the study objective "to compare survival of patients with stage IV CRC who underwent primary tumor resection with the patients who did not have surgery and to determine the prognostic importance of surgery of the primary tumor in patients with stage IV CRC." The study findings were presented in January 2013 at the Gastrointestinal Cancer Symposium in San Francisco, USA. Notably, our study met the criteria for good quality study and scored 9 of 9 for overall survival, in the Newcastle-Ottawa Quality Assessment Scale, the validity scoring for observational study (**Appendices F and O**). The results were published in the Cancer "*Ahmed S, Leis A, Fields A, Chandra-Kanthan S, Haider K, Alvi R, Reeder B, Pahwa P. Survival impact of surgical resection of primary tumor in patients with stage IV colorectal cancer: Results from a large population-based cohort study. Cancer. 2014 Mar 1; 120(5):683-91.*"

4.1 Abstract

Background: Currently, there is very low-quality evidence available regarding benefit of primary tumor resection, in patients with stage IV CRC. In the absence of randomization, the reported benefit may reflect selection of younger and healthier patients with good performance status. A large population-based cohort study was undertaken to determine the survival benefit of primary tumor resection in advanced CRC by eliminating various biases reported in the literature.

Methods: A retrospective cohort study involving patients with stage IV CRC, diagnosed between 1992 and 2005, in the province of Saskatchewan, Canada. Survival was estimated by using the Kaplan-Meier method. Survival distribution was compared by the log-rank test. Cox proportional multivariate regression analysis was performed to determine survival benefit of primary tumor resection by controlling other prognostic variables.

Results: A total of 1378 eligible patients were identified. Their median age was 70 years (range: 22-98) and male: female ratio was 1.3:1; 944 (68.5%) of them underwent primary tumor resection. Among 1378 patients, 42.3% received chemotherapy and 19.1% received second-generation therapy. Patients who underwent surgery and received chemotherapy had median overall survival of 18.3 months (95% CI: 16.6-20) compared with 8.4 months (95% CI: 7.1-9.7) if they were treated with chemotherapy alone ($p<0.0001$). Cox proportional analysis revealed that use of chemotherapy (HR 0.47, 95% CI: 0.41-0.54), primary tumor resection (HR 0.49, 95% CI: 0.41-0.58), second-line chemotherapy (0.47, 95% CI: 0.45-0.64), and metastasectomy (HR 0.54, 95% CI: 0.45-0.64) were correlated with superior survival.

Conclusions: Primary tumor resection improves survival in patients with stage IV CRC, independent of other prognostic variables including age, performance status, comorbid illness and chemotherapy.

4.2 Introduction

Whereas surgery is the primary treatment of localized CRC, resection of the primary tumor in patients with incurable metastatic disease is usually recommended for palliative purposes to manage obstruction, perforation, or bleeding. Only a subset of patients with limited liver and or lung metastases can be cured with multimodality therapy. Complete resection of the primary tumor with metastatic lesions, in these patients, has been associated with durable remission in about 40% cases (1). The role of surgical resection of the primary tumor in patients with newly diagnosed incurable stage IV colorectal cancer remains controversial. Despite uncertain survival benefit, a high rate of surgical resection has been reported in patients with unresectable metastatic disease (2). Currently, there is very low-quality evidence available regarding survival benefit of resection of primary tumor, in patients with stage IV CRC and otherwise unresectable metastatic lesions. Although some have advocated for surgery (3,4), other have failed to demonstrate survival benefit with resection of primary tumor in patients with stage IV CRC (5,6). A recent meta-analysis of literature involving 15 observational studies revealed 31% reduction in mortality (HR: 0.69, 95% CI: 0.61-0.79) with surgical resection of the primary tumor, with an absolute difference in median survival of approximately 4 months (7,8). Notably, comparable survival benefits were noted in studies using newer generation chemotherapy versus older regimen, and in minimally symptomatic or asymptomatic patients versus symptomatic patients. Nevertheless, in the absence of randomization, the reported benefit may reflect selection of younger and healthier patients with good performance status. Taking selection bias into consideration, recent observational studies do not advocate surgery and suggest that outcomes are not compromised, by leaving the primary colon tumor intact, in patients treated with modern chemotherapy (9,10).

To date, no randomized trial has assessed the survival impact of primary tumor resection, in patients with stage IV CRC. In the absence of randomized controlled trial, this study was undertaken to investigate the optimal surgical management of patients diagnosed with stage IV CRC cancer, by controlling for various know confounding factors including age, comorbid illness, performance status and other important prognostic variables.

4.3 Study Objectives

The primary objective of this study was to compare survival of patients diagnosed with stage IV CRC, who underwent primary tumor resection, with that of patients who did not have surgery. The secondary objectives were as follows: 1) to compare survival of patients with stage IV CRC who were treated with chemotherapy and underwent resection of the primary tumor, with the survival of patients who did not have surgery; 2) to compare survival of asymptomatic or minimally symptomatic patients with stage IV CRC, who underwent surgical resection of the primary tumor, with the patients who did not have surgery; and 3) to determine survival benefit of primary tumor resection by controlling for various clinicopathological variables that affect the outcome of patients with metastatic CRC.

4.4 Methods

4.4.1 Study Population

The study protocol was approved by the Research Ethics Board of the University of Saskatchewan, Canada. The study population was composed of a cohort of patients 18 years or older, with histologically documented adenocarcinoma of colon and rectum, intact primary tumor, and evidence of metastases (stage IV colorectal cancer), who were diagnosed between the period of 1992 and 2005, in the province of Saskatchewan. Patients with other histological diagnosis or with other active secondary malignancy or with fixed inoperable primary tumor at the time of diagnosis were excluded. The Saskatchewan Cancer Registry database is prospectively collected and updated. Eligible patients were identified from the Saskatchewan Cancer Registry. All medical records were individually reviewed, and data was abstracted by a trained research associate, using a pre-specified and validated abstraction sheet.

4.4.2 Sample Size

Because a high rate of primary tumor resection has been reported in the literature, assuming two-thirds of patients in Saskatchewan underwent resection of primary tumor, a ratio of 1:2 was used for the non-resection group versus the resection group. Using a power of 90%, type 1 error of 0.05 with two sided P-value, and survival difference of 20% in the two groups (resection vs. non-resection) with a follow up period of 60 months, a total sample size of 959 patients was estimated (326 in the non-resection group and 633 patients in the resection group).

4.4.3 Analysis of Primary and Secondary Endpoints

Overall survival was defined as “time from the diagnosis of stage IV CRC to death from any cause.” Patients who did not die at the end of the follow-up period, or were lost to follow-up during the study, were censored at the last date they were known to be alive. Survival of the entire cohort and subgroups was estimated by using the Kaplan-Meier method. Survival distribution of different groups was compared by the log-rank test. The overall significance level was set at 0.05. A multivariate analysis was performed to determine the prognostic significance of primary tumor resection in patients with stage IV CRC. The Cox proportional hazard model was used and the

hazard ratio and its 95% CI were estimated. Following variables were examined with respect to their prognostic significance: Resection of primary tumor, age (<65 vs. ≥65), gender, major comorbid illness, ECOG performance status (<2 vs. ≥2), smoking, sodium level (≤135 mEq/l vs. >135 mEq/l), serum creatinine (≥120 vs. <120 mm/l), BUN (≥8 vs. <8 mm/l), albumin (≥36 vs. <36 g/l), bilirubin (≥26 vs. <26 mm/l), alkaline phosphatase (≥120 vs. <120 U/l), hemoglobin (≥120 vs. <120 g/l), WBC (≥11 vs. <11 x 10^9/l), platelet (≥450 vs. <450 x10^9/l), CEA (≥6 vs. <6 mcg/l), site (colon vs. rectal), grade (Grade 3 vs. <3), symptomatic disease, extrahepatic metastases, disease burden (patients with metastasis confined to one organ or site vs. metastases in more than one organ or site), metastasectomy, use of chemotherapy, second-line chemotherapy and second-generation chemotherapy. For the variables examined in the final mathematical model, the proportional hazards assumption was assessed using log-log survival curves.

The asymptomatic or minimal symptomatic disease was defined as absence of obstruction, perforation or bleeding. Major comorbid illnesses were defined as presence of coronary artery disease, diabetes mellitus, chronic renal insufficiency, chronic obstructive lung disease and others (uncontrolled hypertension, peripheral vascular disease, stroke or transient ischemic attack, interstitial lung disease, congestive heart failure, cardiac arrhythmia, among others). Post-operative mortality was defined as death that occurred within 30 days of surgery. Second-generation therapy was defined as use of bevacizumab or the anti-epidermal growth factor receptor antibodies cetuxiamb or panitumumab and or oxaliplatin or irinotecan based therapy (FOLFOX or FOLFIRI).

All variables with P<0.05, on univariate analysis, were examined, in a multivariate model, to assess their correlation with survival. A best-fitted but a most parsimonious model was built by identifying the important predictors for survival. The likelihood ratio test and *t* test were used to determine if the addition of independent variables of interest add significantly to the prediction of survival in the model. Test for interaction was performed for resection of primary tumor and all the variables that were significantly correlated with survival. An imputation technique was used for missing data. A two-sided P-value of <0.05 were considered to be statistically significant. SPSS versions 20.0 & 21.0, were used for statistical analysis (SPSS Inc. Chicago, IL).

4.5 Results

4.5.1 Patients' Characteristics

A total 1378 eligible patients were identified (**Figure 4.1**). Their median age was 70 years (range: 22-98) and male-to-female ratio was 1.3:1. Seven-hundred eighty one (56.7%) patients were male, 1,005 patients (72.9%) had ECOG performance status of <2, 856 (62.1%) patients had a comorbid illness, and 204 (14.8%) patients had a history of secondary malignancy. Patients' characteristics are described in **Table 4.1**. A significance difference was noted between the two groups with respect to age, performance status, extrahepatic disease, mean serum albumin, alkaline phosphatase, bilirubin, BUN, CEA, and WBC count. As expected, patients in the surgical group tended to be younger with better performance status and organ function and less likely to have extrahepatic disease.

Of 1378 patients, 29.5% had rectal or rectosigmoid tumor (rectal, 20.1%, rectosigmoid, 9.4%). One hundred ninety-seven (14.3%) patients had mucinous tumor. A total of 544 patients (39.5%) were symptomatic, among whom 454 (83%) had obstructive symptoms, 87 (16%) developed bowel perforation, and 56 (10%) had major bleeding (drop in hemoglobin of ≥20 gm/l or required blood transfusion). Symptoms were not mutually exclusive. One thousand thirty-eight (75.3%) patients had liver metastases and 698 (50.7%) had extrahepatic metastases. Among 698 patients with extrahepatic disease, 217 (31%) had lung metastases, 205 (29.3%) had peritoneal involvement, 31 (4.4%) had bony metastases, and 9 (1.3%) patients had documented brain metastases.

4.5.2 Interventions

Of 1378 patients, 944 (68.5%) underwent resection of the primary tumor and 434 (31.5%) did not have surgery. Five hundred and eighty-three (42.3%) patients received 5-fluorouracil based chemotherapy (**Table 4.1**). Of 583 patients, 222 (38%) patients, on progression, were treated with second-line chemotherapy mostly oxaliplatin- and/or irinotecan-based therapy with or without biologics. A significantly higher number of patients in the surgical group were treated with chemotherapy, or received second-line or newer generation chemotherapy. Likewise, a significantly higher number of patients in the surgical group underwent metastasectomy.

4.5.3 Follow-up and Survival

Median follow-up time was 7.1 months (interquartile range 2.5-17.5 months) for the whole cohort. There was no loss of follow-up in both groups. Median survival of whole cohort of patients who underwent primary tumor resection was 10.6 months (95% CI: 9.5-11.7) compared with 3.0 months (95% CI: 2.5-3.5) of patients who did not have surgery (P<0.0001). Overall 30-day mortality rate in the surgical group was 6.6%. Median survival of cohort of patients who received chemotherapy was 15.9 months (95% CI: 14.5-17.3). Patients who underwent primary tumor resection and received chemotherapy had median overall survival of 18.3 months (95% CI: 16.6-20) compared with 8.4 months (95% CI: 7.1-9.7) if they were treated with chemotherapy alone (p<0.0001; **Figure 4.2)**. In a subgroup of patients who were treated with second-generation chemotherapy, median survival of patients who underwent primary tumor resection was 24.6 months (95% CI: 20.2-29.0) versus 11.0 months (95% CI: 7.8-14.3) if they did not have surgery (p<0.0001).

The median survival of subcohort of 834 asymptomatic or minimally symptomatic patients who were treated with chemotherapy and underwent primary tumor resection was 18.3 months (95% CI: 16.6-20.0) compared with 8.4 months (95% CI: 7.1-9.7) if they did not have surgery (p<0.0001) [**Figure 4.3**]. After excluding the patients who underwent metastasectomy, median survival of patients who underwent primary tumor resection was 15.2 months (95% CI: 13.5-16.9) compared with 8.3 months (95% CI:71.-9.6) if they did not have surgery (p<0.0001).

4.5.4 Multivariate Analysis

On univariate analysis various clinicopathological factors were identified that were correlated with survival (**Table 4.2**). Among them, ECOG performance status of >1 was most strongly correlated with a poor survival, whereas use of chemotherapy was most strongly correlated with better survival. Tests for interaction between surgical resection of primary tumor and age, performance status, CEA level, second-line therapy or more than one metastatic sites were significant. Primary tumor resection was associated with better survival in younger patients, patients with good performance status, normal CEA level, patients treated with second-line therapy and patients with one metastatic site. For instance, unadjusted HR for mortality in patients 65 years or younger was 0.28 (95% CI: 0.22-0.36) compared with 0.48 (95% CI: 0.42-0.55) in older patients in relationship with primary tumor resection. Likewise, with respect to surgery, unadjusted HR for mortality in patients with metastasis confined to one organ or site was 0.36 (95% CI 0.31-0.42) compared with HR of 0.56 (95% CI 0.45-0.68) in patients with metastases involving more than one organ or site. Cox proportional multivariate regression analysis using interaction terms revealed that use of chemotherapy (HR 0.47, 95% CI: 0.41-0.54), primary tumor resection (HR 0.49, 95% CI:0.41-0.58), second-line chemotherapy (0.47, 95% CI: 0.45-0.64), and metastasectomy (HR 0.54, 95% CI: 0.45-0.64) were correlated with a favorable survival in patients with advanced CRC, whereas older age, poor performance status, low albumin, elevated bilirubin, elevated alkaline phosphatase, anemia, leukocytosis, colonic primary, and Grade 3 tumor were correlated with inferior survival (**Table 4.3, Figure 4.4**). After controlling for the other significant or clinically important variables, only the interactions between primary tumor resection and second-line therapy, or more than 2 metastatic sites, were significant. Because approximately 86% patients who were treated with second-line therapy received second-generation chemotherapy, in order to avoid multicollinearity, second-generation therapy was not included in the final model. In a secondary analysis, after excluding 198 patients who underwent metastasectomy, primary tumor resection significantly correlated with better survival (HR, 0.43; 95% CI: 0.41-0.52). After adjusting for other important prognostic variables in a Cox proportional multivariate model, the HR for survival with primary tumor resection was 0.54 (95% CI: 0.48-0.62).

4.6 Discussion

This is the first large population-based cohort study that demonstrated survival advantage of surgical resection of primary tumor, in patients with stage IV CRC, independent of other important prognostic factors including age, performance status, comorbid illness and chemotherapy. Several studies previously have shown survival benefit of resection of the primary tumor. However, many studies did not provide baseline characteristics of patients in each group, whereas others showed significant differences between the two groups and failed to control for the differences (7,8). Hence, validity of survival benefit observed in these studies has been questioned and is believed to be biased by the selection of healthier and younger patients for surgery. Despite significant differences in the baseline characteristics between the two groups in the study cohort, when these variables were included in a multivariate model, primary tumor resection remained an important prognostic variable and was associated with 51% relative reduction in mortality when adjusted for age, performance status, comorbid illnesses, chemotherapy, metastasectomy, second-generation chemotherapy, disease burden and various other important prognostic factors. Notably, survival

differences between the two groups (resection versus non-resection), within the study cohort and various sub-groups, were consistently more than 6 months (range: 7.6 to 13.6 months).

There is a general agreement that patients with evidence of perforation, significant obstruction, or uncontrolled bleeding should undergo resection of the symptomatic tumor. However, primary tumor resection, in patients with asymptomatic or minimally symptomatic disease and otherwise unresectable metastases, is not recommended. In the study cohort, about 60% of patients, were asymptomatic or had minimal symptoms. These patients had comparable survival benefit with surgical intervention. Moreover, the surgical intervention was independently associated with a survival benefit, after controlling for other important prognostic variables (analysis is not shown).

Modern chemotherapy regimens incorporating novel cytotoxic and biologic agents have been associated with high response rates of 40-50% (11). Although only about 19% of the study cohort was treated with modern chemotherapy, the magnitude of benefit of surgical intervention was substantially higher in a subgroup of patients who were treated with second-generation and or second-line chemotherapy. In the study cohort, less than 2% of patients received biologics therapeutics including bevacizumab or the anti-epidermal growth factors receptor (EGFR) monoclonal antibodies such as cetuximab or panitumumab, hence, a subgroup analysis was not feasible. Nevertheless, a retrospective analysis of a Dutch trial that primarily assessed the efficacy of combination of chemotherapy and biologics, demonstrated a superior survival with surgical resection of primary tumor (3). In a subgroup of patients who underwent primary tumor resection, a significantly better median overall survival of 20 months was observed compared with 13.4 months for the patients in the non-resection group, ($P<0.0001$; HR 0.65, 95% CI 0.52–0.80). Likewise, a pooled analysis of four French trials including study involving targeted therapy demonstrated 37% reduction in mortality (HR: 0.63, 95% CI: 0.53-0.75) with primary tumor resection (12). Therefore, evidence supports comparable benefit of resection of the primary tumor in patients treated with modern regimens. Notably, the tests for interactions between primary tumor resection and second-line therapy or disease burden were significant after adjusting for other variables, suggesting that patients who received second-line therapy or who had metastasis confined to one organ or site tend to get most benefit from surgical removal of primary tumor.

The underlying mechanism of potential survival benefit with removal of the primary tumor is not known. It is well known that surgical resection of primary tumor, in some cancers, such as advanced ovarian and renal cell cancer, has been associated with significant survival benefit (13,14). The primary tumor may secrete cytokines that promote tumor growth and reduce response to cytotoxic agents (15). Moreover, noncurative resection of the primary tumor in patients with advanced cancer may prevent local tumor complications, improve disease control by reducing the tumor bulk, and tolerance to systemic therapy.

A variety of clinical parameters such as age, performance status, WBC count, hemoglobin, serum albumin, alkaline phosphatase, CEA, pathological grading or localization of the primary tumor have been identified as prognostic markers in patients with stage IV CRC (16-19). In the study cohort, in addition to resection of primary tumor, use of 5-FU based chemotherapy, second-line chemotherapy, metastasectomy, older age, performance status, colonic primary, high-grade tumor; and baseline elevated alkaline phosphatase, bilirubin, anemia and leukocytosis were independently

correlated with survival. As expected, significantly more patients were diagnosed with a rectal or rectosigmoid tumor, in the control group. Despites that, for reason not clear, patients with rectal or rectosigmoid tumors compared with more proximal tumor had better survival. Frerrand and colleagues reported a similar observation in their retrospective analysis of FFCD 9601 trial (20). These differences in patient survival were maintained after exclusion of patients with rectal primary.

To our knowledge, this is the only large population-based cohort study that examined age, co-morbid illness, performance status, serum albumin, and other important clinical variables in a multivariate model and demonstrated survival benefit of primary tumor resection independent of other variables. One of the limitations of the current study is that it did not assess BRAF mutation, which is an important prognostic marker in stage IV CRC. In addition, disease burden was not measured in patients with single versus multiple site metastases. Hence, better survival secondary to selection of patients with low disease burden, who have better prognosis, cannot be eliminated.

In summary, this well-designed population-based cohort study, with minimal selection and information biases, supports primary tumor resection in patients with stage IV CRC, independent of other important prognostic factors. In addition to systemic therapy and metastasectomy, primary tumor removal was associated with better survival. A Dutch randomized controlled trial (CARIO 4) assessing survival benefit of primary tumor resection in patients with advanced CRC, with estimated improvement in median survival from 13 month to 19 months, once completed, will be valuable to confirm our findings (21).

4.7 References

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Table 4.1: Baseline characteristics of patients in the two groups: patients who underwent primary tumor resection and the control group who did not have surgery.

Variables Mean ±standard deviation (%)	Total patients N=1378	Surgical Group N=944	Control N=434	P value
Age years	68.8±12.2	68.4±12.6	70±11.5	0.018
Age >65 years	925 (67.1)	617 (65)	308 (71)	0.04
Male	781 (56.7)	523 (55.4)	258 (59.4)	0.16
Comorbid illness	514 (37.3)	362 (38.3)	152 (35)	0.26
ECOG PS ≥2	373 (27.1)	207 (21.9)	166 (38.2)	<0.001
Active smoker	178 (12.9)	118 (12.5)	60 (13.8)	0.38
Rectal tumors*	407 (29.6)	242 (25.6)	165 (38.1)	<0.001
Grade 3 cancer	271 (19.7)	202 (21.4)	69 (15.9)	0.01
Extra-hepatic disease	698 (50.7)	455 (48.2)	243 (56)	0.004
Metastases≥2 sites	408 (29.6)	247 (26.2)	161 (37.1)	<0.001
Symptomatic disease	544 (39.5)	423 (44.8)	121 (27.9)	<0.001
Albumin g/l	34.1±5.4	34.7±5.6	32.8±4.8	<0.001
Alkaline phosphatase	192±242	179.6±239.9	221.1±245.9	0.003
Bilirubin mm/l	13.7±24.6	11.9±18.7	17.5±33.7	<0.001
BUN	6.0±4.9	5.7±4.3	6.6±5.8	0.003
Creatinine	89.2±32.1	88.4±32.2	90.9±31.9	0.19
CEA	260±1554	197±894	398±2433	0.026
Hemoglobin g/l	117.9±15.8	117.8±15.4	118.2±16.5	0.65
Sodium	138±3	138±3	137±3.9	0.77
White blood cell count	9.2±4.0	8.9±3.9	9.8±4.1	<0.001
Received 5FU –based chemotherapy	583 (42.3)	469 (49.7)	114 (19.6)	<0.001
Received 2nd line chemotherapy	222 (16.1)	185 (19.6)	37 (8.5)	<0.001
Received 2nd generation chemotherapy	263 (19.1)	203 (21.5)	60 (13.8)	<0.001
Received radiation	190 (13.8)	124 (13.1)	66 (15.2)	0.17
Metastasectomy	198 (14.4)	183 (19.4)	15 (3.5)	<0.001

*Rectum or recto-sigmoid disease

Table 4.2: Univariate correlation between various clinicopathological variables and overall survival in patients with stage IV colorectal cancer.

Variables	Unadjusted Hazard Ratio	95% Confidence Interval	P value
Age >65 years	1.45	1.29-1.62	<0.001
Male	1.04	0.93-1.16	0.52
Comorbid illness	1.21	1.09-1.36	0.001
ECOG PS ≥2	2.51	2.22-2.84	<0.001
Active smoker	1.16	1.04-1.29	0.008
Extra-hepatic disease	1.10	0.99-1.23	0.078
Symptomatic disease	1.10	0.98-1.22	0.10
Albumin <35 g/l	2.20	1.96-2.46	<0.001
Alkaline phosphatase ≥ 120 IU	1.52	1.35-1.71	<0.001
Bilirubin ≥26 mm/l	2.46	1.95-3.10	<0.001
Sodium <136 meq/l	1.51	1.29-1.76	<0.001
BUN ≥8 mm/l	1.29	1.08-1.54	0.008
Creatinine ≥120 mm/l	1.31	1.07-1.60	0.009
CEA ≥ 6 mcg/l	2.42	2.03-2.87	<0.001
Hemoglobin <120 g/l	1.46	1.31-1.63	<0.001
Platelets ≥450 x 10^9/l	1.03	0.88-1.19	0.72
White blood cell count ≥11 x 10^9/l	1.79	1.56-2.06	<0.001
Colon Cancer	1.18	1.05-1.33	0.005
Grade 3 cancer	1.26	1.10-1.45	0.001
Mucinous cancer	0.97	0.83-1.13	0.70
Metastases ≥2 sites	1.5	1.3-1.6	<0.001
Received 5-FU-based chemotherapy	0.33	0.29-0.37	<0.001
Received 2nd line chemotherapy	0.42	0.36-0.48	<0.001
Received 2nd generation chemotherapy	0.45	0.89-0.52	<0.001
Surgical resection of primary tumor	0.40	0.36-46	<0.001
Metastasectomy	0.37	0.31-0.43	<0.001
Diagnosed ≥ Jan 1st 2000	0.94	0.85-1.1	0.94

Table 4.3: Multivariate correlation between various clinicopathological variables and overall survival, using Cox regression analysis, in patients with stage IV colorectal cancer.

Variables	Hazard Ratio	95% Confidence Interval	P value
Age >65 years	1.37	1.10-1.70	0.005
Male	1.02	0.92-1.15	0.68
Comorbid illness	1.09	0.97-1.22	0.14
ECOG PS ≥2	1.44	1.26-1.64	<0.001
Albumin <35 g/l	1.50	1.32-1.71	<0.001
Alkaline phosphatase ≥ 120 IU	1.41	1.23-1.61	<0.001
Bilirubin ≥26 mm/l	1.47	1.15-1.89	0.002
Hemoglobin <120 g/l	1.17	1.04-1.32	0.01
White blood cell count ≥11 x 10^9/l	1.33	1.15-1.55	<0.001
Colon Cancer	1.20	1.06-1.35	0.004
≥Two metastatic sites	1.02	0.83-1.23	0.88
Grade 3 cancer	1.37	1.19-1.57	<0.001
Received 5-FU-based chemotherapy	0.47	0.41-0.54	<0.001
Received 2nd line chemotherapy	0.47	0.33-0.67	0.001
Surgical resection of primary tumor	0.49	0.41-0.58	<0.001
Metastasectomy	0.54	0.45-0.64	<0.001

*Median value was used for cut off.

Figure 4.1: Flow diagram of eligible patients with stage IV colorectal cancer patients who underwent surgical resection of the primary tumor or did not have surgery.

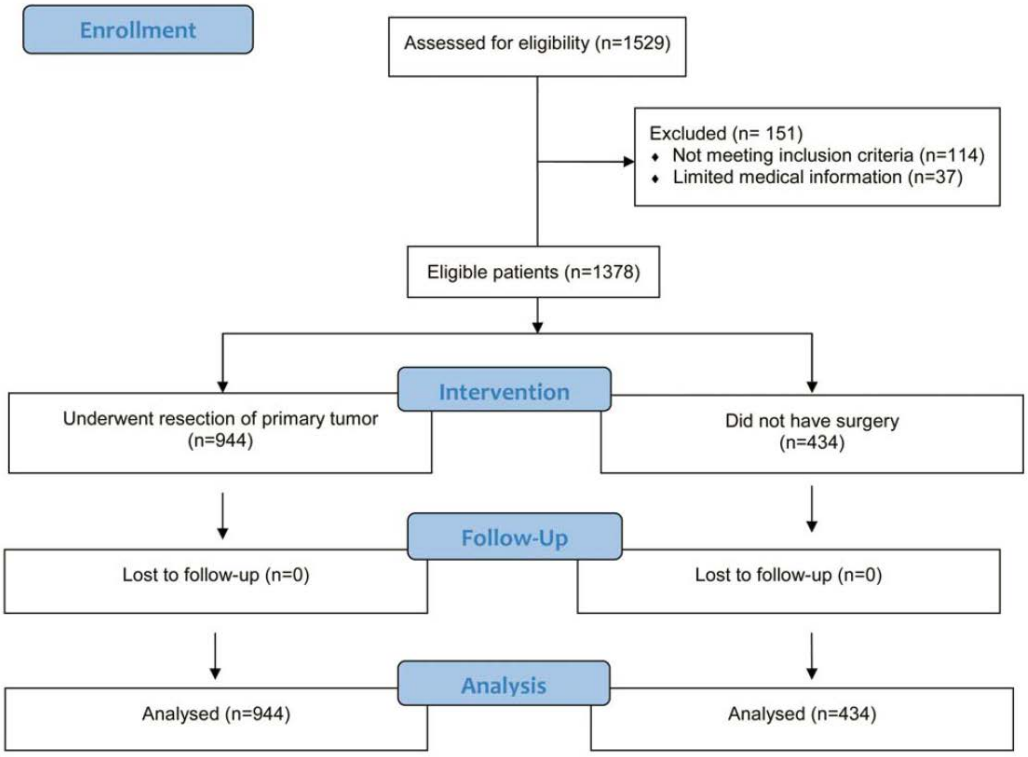


Figure 4.2: Kaplan-Meier survival curves are shown of (4.2A) patients who received chemotherapy and underwent resection of the primary tumor versus no surgery or (4.2B) patients who received second-generation chemotherapy and underwent resection of the primary tumor versus no surgery.

Figure 4.2A:

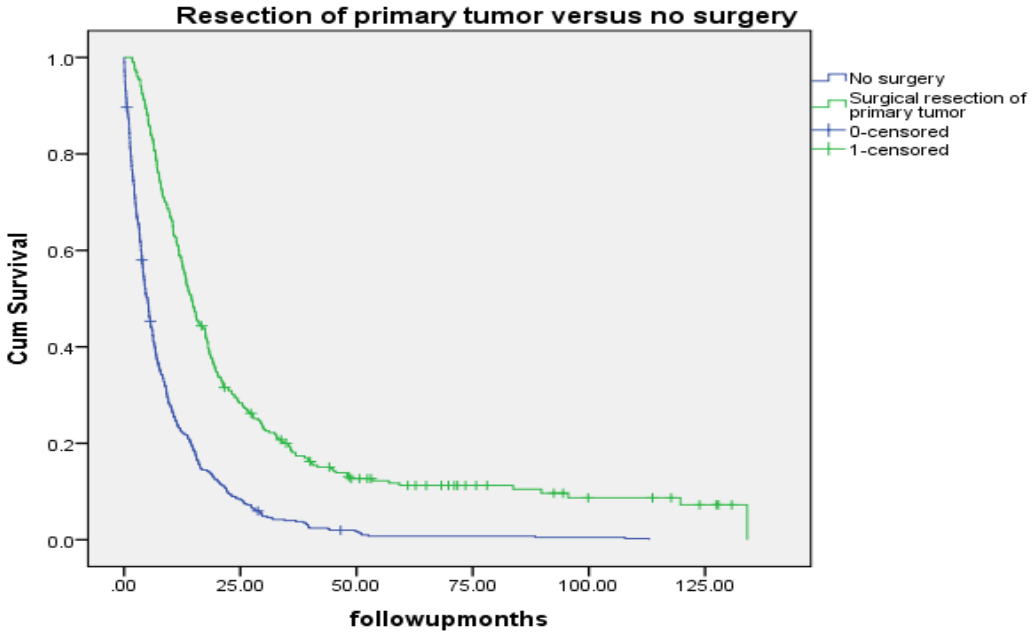


Figure 4.2B:

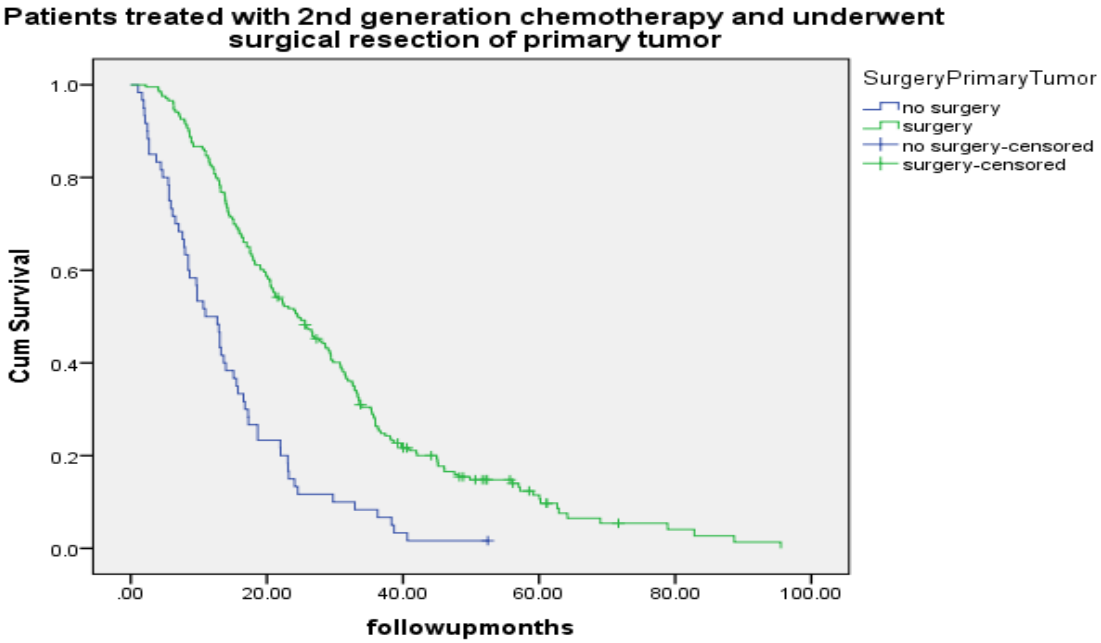


Figure 4.3: Kaplan-Meier survival curves of (3A) asymptomatic patients who received chemotherapy and underwent resection of the primary tumor versus no surgery or (3B) asymptomatic patients who received second-generation chemotherapy and underwent resection of the primary tumor versus no surgery.

Figure 4.3A:

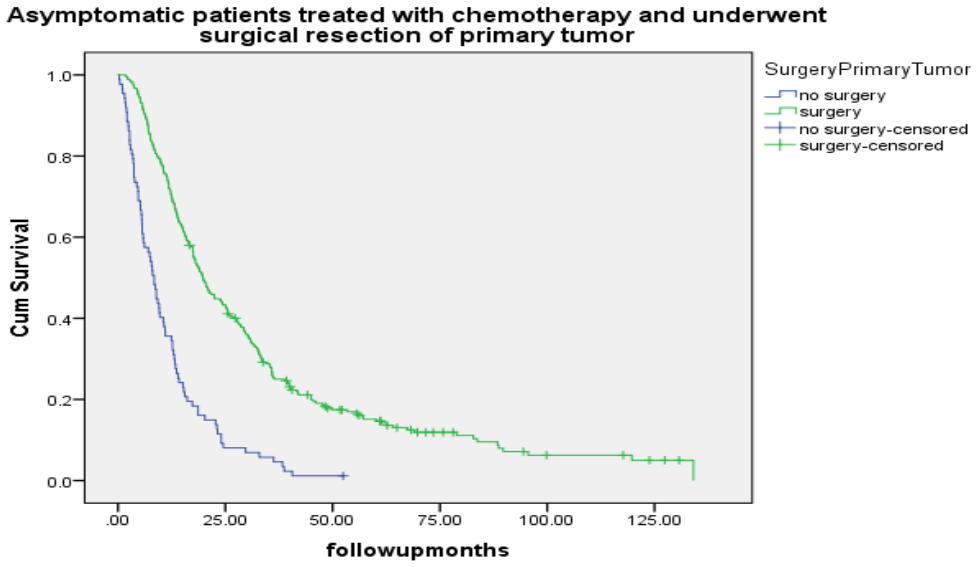


Figure 4.3B:

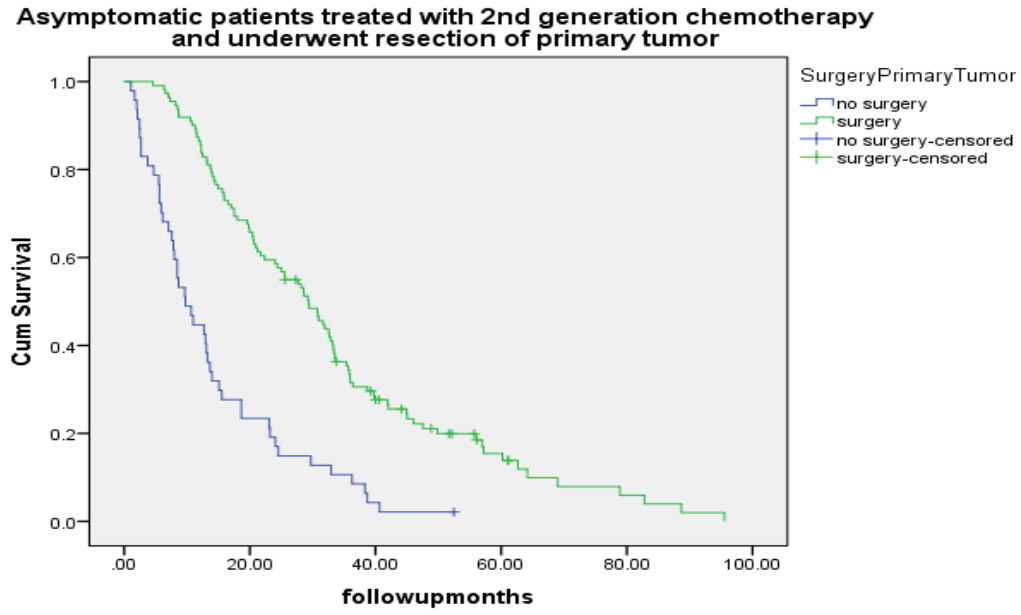
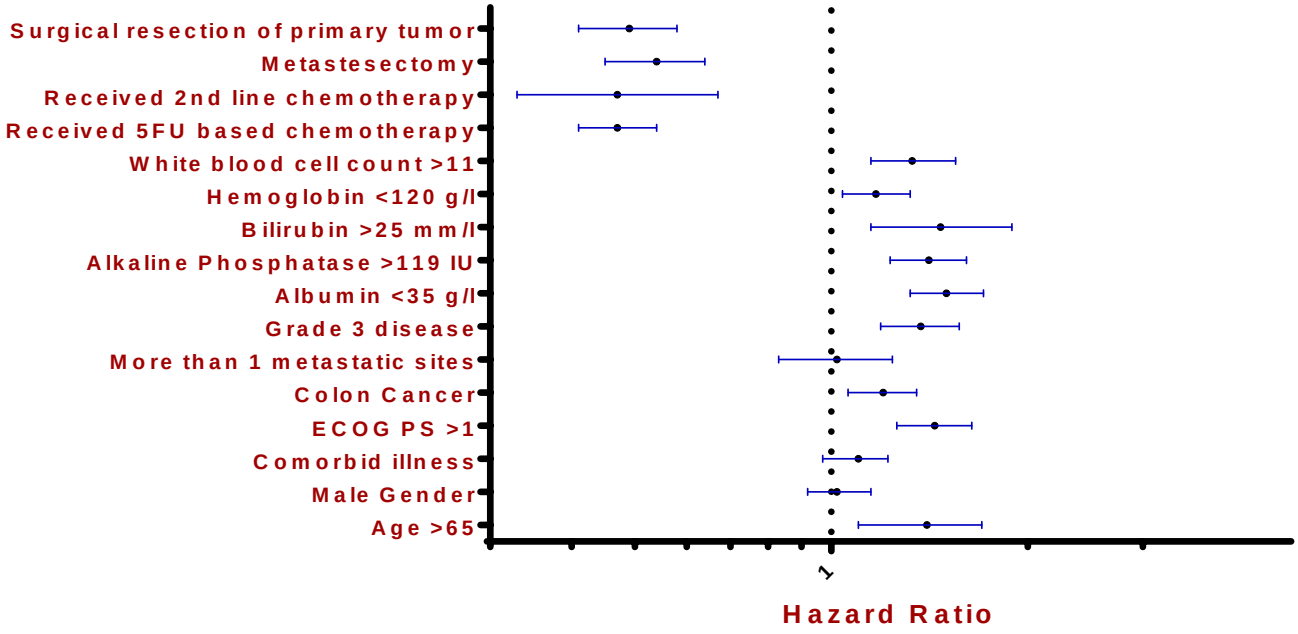


Figure 4.4: Adjusted hazard ratios for survival in relationship with various clinicopathological variables in patients with advanced colorectal cancer.



CHAPTER 5 – COHORT STUDY (1992-2005): PRIMARY TUMOR RESECTION IN ASYMPTOMATIC OR MINIMALLY SYMPTOMATIC PATIENTS

Our well designed and good quality large population based cohort study, with minimal selection and information biases, supports surgical resection of the primary tumor in patients with stage IV CRC, independent of other important prognostic factors. In addition to systemic therapy and metastasectomy, primary tumor removal was associated with better survival. Nevertheless, the study cohort was inclusive of patients with symptomatic primary tumor, a group of patients who may get benefit from resection of the primary tumor.

The current chapter focuses on the study objective "to determine survival advantage of primary tumor resection in a subcohort of patients with stage IV CRC and minimally symptomatic or asymptomatic primary tumor". In the present study we examined the prognostic role of surgery in a cohort of patients with stage IV CRC and asymptomatic or minimally symptomatic primary tumor. The study findings were presented in June 2014 at the American Society of Clinical Oncology Poster Discussion session in Chicago, USA. The results were published in the Clinical Colorectal Cancer "*Ahmed S, Fields A, Pahwa P, Chandra-Kanthan S, Zaidi A, Le D, Haider K, Reeder B, Leis A. Surgical Resection of Primary Tumor in Asymptomatic or Minimally Symptomatic Patients With Stage IV Colorectal Cancer: A Canadian Province Experience. Clin Colorectal Cancer. December 2015 Volume 14, Issue 4, Pages e41–e472015 Jun 6. pii: S1533-0028(15)00066-3. doi: 10.1016/j.clcc.2015.05.008.*"

5.1 Abstract

Background: Surgical resection of the primary tumor in patients with stage IV CRC remains controversial. Survival benefit reported in literature has been attributed to the selection of younger and healthier patients with good performance status. We have recently reported that primary tumor resection improves survival of patients with stage IV CRC. In this study we examined survival benefit of surgery in patients with asymptomatic or minimally symptomatic primary tumor.

Methods: A cohort of patients with stage IV CRC and asymptomatic or minimally symptomatic primary tumor, who were diagnosed during the period of 1992 to 2005, in the province of Saskatchewan, Canada, was evaluated. The Kaplan-Meier method was used to determine survival. A multivariate Cox proportional hazard regression analysis was performed to determine prognostic importance of resection of primary tumor and other important clinicopathological variables.
Results: A total of 834 patients with median age of 70 years (22-93) and M:F of 58:42 were identified. Among them 521 (63%) patients underwent surgery and 43.3% received chemotherapy.

Patients who underwent surgery and received chemotherapy had median overall survival of 19.7 months (95% CI: 16.9-22.6) compared with 8.4 months (95% CI: 6.9-10.0) if they did not have surgery ($p<0.0001$). On multivariate analysis, 5FU-based chemotherapy (HR 0.43; 95% CI: 0.36-0.53), primary tumor resection (HR 0.47; 95% CI 0.39-0.57), metastasectomy (HR 0.48; 95% CI 0.38-0.62), and second-line chemotherapy (HR 0.72; 95% CI 0.58-0.92) were correlated with superior survival. A test for interaction between ≥1 metastatic sites and surgery was significant, which suggests a larger benefit of surgery in patients with stage IVa disease.

Conclusions: Results of this large population-based cohort study suggests that primary tumor resection in asymptomatic or minimally symptomatic patients with stage IV CRC improved survival independent of other prognostic variables. The benefit was more pronounced in Stage IVa disease.

5.2 Introduction

Colorectal cancer is one of the most common cancers and is the leading cause of cancer-related death in the Western world. In 2008 over 1.2 million new cases were diagnosed and 608,700 deaths were attributed to CRC (1). Approximately 20% of patients with CRC present with metastases or Stage IV disease but less than one-quarter of them are suitable candidate for radical resection. The role of surgery in the management of stage IV CRC has evolved. Although the benefit of metastasectomy is well established in the setting of oligometastases, primary tumor resection in patients with unresectable metastases and asymptomatic or minimally symptomatic primary tumor remains controversial. There is still considerable uncertainty, as to whether patients with advanced CRC with little or no symptoms related to the primary tumor should undergo surgery before systemic therapy (2-4). Because of the lack of level I evidence, the current guidelines do not support surgical resection of the primary tumor in asymptomatic or minimally symptomatic patients, and recommend surgery if there is a consideration of complete resection of the metastatic disease. A recent meta-analysis revealed that primary tumor resection in patients with stage IV CRC was associated with a lower mortality risk (odd ratio, 0.28; 95 % CI: 0.17–0.47), which translates into a difference in mean survival of 6.4 months favoring resection (4). Similar results were reported by our research group. A meta-analysis of 15 observational studies showed better survival of patients who underwent primary tumor resection (HR for mortality: 0.69, 95% CI: 0.61-0.79) [2]. Nevertheless, most studies failed to adjust for selection of younger and healthier patients with good performance status. We conducted a large population based cohort study and showed that primary tumor resection in patients with stage IV CRC improves survival, independent of age, performance status, comorbid illness and chemotherapy (5). The study cohort was inclusive of patients with symptomatic primary tumor. In the present study we examined the prognostic role of surgery in a cohort of patients with stage IV CRC and asymptomatic or minimally symptomatic primary tumor.

5.3 Methods

5.3.1 Eligibility Criteria

The study protocol was approved by the Institutional Review Board at the University of Saskatchewan. The study population was comprised of a cohort of adult patients, with histologically documented stage IV adenocarcinoma of colon and rectum, diagnosed over a period of fourteen years (January 1992 to December 2005), in the province of Saskatchewan, Canada. Patients with other histological diagnosis including neuroendocrine tumor or with other active secondary malignancy at the time of diagnosis were excluded. In addition, patients with previous diagnosis of early stage CRC who were treated with curative resection and subsequently developed metastatic disease were excluded. Eligible patients were identified using Saskatchewan Cancer Registry – Canada. Individual medical records were reviewed and information was extracted using a validated abstraction sheet by a trained research associate. The asymptomatic or minimal symptomatic disease was defined as absence of obstruction, perforation or major bleeding (decrease in hemoglobin of ≥20 gm/l or required blood transfusion). The major comorbid illnesses were defined as presence of coronary artery disease, congestive heart failure, diabetes mellitus, chronic renal insufficiency, uncontrolled hypertension, peripheral vascular disease, stroke, chronic obstructive lung disease, interstitial lung disease, connective tissue disease, dementia, symptomatic multiple sclerosis, cirrhosis of the liver, and AIDS among others. Performance status information was collected using the ECOG scale. The Karnofsky performance status score was transformed into the ECOG scale.

5.3.2 Statistical Analysis

The baseline characteristics of patients were compared using the chi square test. Continuous variables were examined using the Student *t* test. Descriptive data are reported in mean (standard deviation) and median (range). Overall survival (OS) was the primary end point and was defined as time from the diagnosis of stage IV CRC to death from any cause or the date at which patient was last confirmed to be alive. Survival was estimated using the Kaplan-Meier method. Survival distribution of different groups was compared using the log-rank test. The overall significance level was set at 0.05.

A multivariate Cox proportional hazard regression analysis was performed to determine relationship between survival and resection of the primary tumor and HR and its 95% CI were estimated. The following variables were examined with respect to their prognostic significance: Resection of the primary tumor, old age (<65 vs. ≥65), male sex, major comorbid illness, ECOG performance status (<2 vs. ≥2), smoking, hyponatremia (≤135 mEq/l vs. >135 mEq/l), renal insufficiency (serum creatinine ≥120 vs. <120 um/l), elevated BUN (≥8 vs. <8 mm/l), hypoalbuminemia (albumin ≥36 vs. <36 g/l), hyperbilirubinemia (≥26 vs. <26 um/l), increased alkaline phosphatase (≥120 vs. <120 IU/l), anemia (≥120 vs. <120 g/l), leukocytosis (≥11 vs. <11 x 10^9/l), thromobocytosis (≥450 vs. <450 x10^9/l), increased CEA (≥6 vs. <6 mcg/l), disease site (colon vs. rectal), high-grade tumor (Grade 3 vs. <3), extra-hepatic metastases, number of metastatic site (Stage IVa vs. > Stage IVb), metastasectomy, use of any fluoropyrimidine chemotherapy, second-line chemotherapy and second-generation (oxaliplatin or irinotecan ±

bevacizumab) chemotherapy. A univariate analysis was performed to assess relationship between survival and individual clinicopathological variables. All variables that were significantly correlated with survival were fitted into a multivariate model. The proportional hazards assumption was assessed using log-log survival curves for all variables examined in the model. SPSS (SPSS Inc. Chicago, IL) versions 21.0 and STATA MP (StataCorp College Station, TX) version 13.1 were used for statistical analysis.

5.4 Results

A total 834 patients with stage IV CRC who were asymptomatic or minimally symptomatic from the intact primary were identified. Four hundred and fifty-four patients, who were diagnosed during the study period, were excluded because of the presence of major symptoms from the underlying primary tumor. The median age of eligible patients was 70 years (range: 22-93) and male: female ratio was 58:42. Twenty-six percent patients had ECOG performance status of $\geq$2 and 62% had one or more than one comorbid illness. Of 834 patients, 521 (63%) underwent resection of the primary tumor and 313 (43.3%) patients did not have surgery. Patient characteristics are described in **Table 5.1**. There were statistically significance differences between the two groups with respect to age, performance status, serum albumin, alkaline phosphatase, bilirubin, CEA, sodium, white blood cell count, rectal tumor, tumor grade, number of metastatic sites, use of chemotherapy and metastasectomy. For example, in the surgical group, 54.9% and 4.8% patients compared with 79.9 % and 9.3% in the control group had low serum albumin and increased bilirubin levels, respectively. Overall, 32.7 % patients had rectal tumor, 29.9% in the surgical group compared with 37.4% in the control group (p=0.027).

Median OS of patients who received chemotherapy was 16 months (95% CI: 13.8-18.2). Patients who underwent primary tumor resection and received 5-fluorouracil/leucovorin had median OS of 19.7 months (95% CI: 16.9-22.6) versus 8.4 months (95% CI: 6.9-10.0) if they did not have surgery (p<0.0001) [**Figure 5.1A**]. Patients who received oxaliplatin- or irinotecan-based chemotherapy and underwent surgery had median OS of 29.4 months (95% CI: 24.2-34.5) compared with 16.0 months (95% CI: 13.2-18.9) when surgical resection of the primary tumor was not performed (p<0.001) [**Figure 5.1B**]. Patients with rectal cancer who underwent surgery and received any chemotherapy had median OS of 22.5 months (95%CI: 16.8-28.1) compared with 8.4 months (95% CI: 4.5-12.4) with no surgery (p<0.001). Conversely, patients with colon cancer who underwent surgery and received any chemotherapy had median OS of 18.0 months (95%CI: 14.6-21.5) compared with 8.1 months (95% CI: 5.2-11.0) if they did not have primary tumor resection (p<0.001). The 30-day mortality rate of all patients who underwent surgical intervention was 4.8%.

In univariate analysis several clinicopathological variables were correlated with survival (**Table 5.2**). Among them, use of any chemotherapy, second-line chemotherapy, metastasectomy, primary tumor resection, age, comorbid illness, performance status, tumor location were correlated with survival. In multivariate analysis 5FU-based chemotherapy (HR 0.43; 95% CI: 0.36-0.53), primary tumor resection (HR 0.47; 95% CI: 0.39-0.57), metastasectomy (HR 0.48; 95%CI: 0.38-0.62), and second-line chemotherapy (HR 0.72; 95% CI: 0.58-0.92) were correlated with a superior survival and increased bilirubin (HR 1.48; 95% CI: 1.11-1.62), low albumin (HR 1.48; 95% CI: 1.25-1.75), ECOG performance status $\geq$2 (HR 1.36; 95% CI: 1.15-1.62), high-grade tumor (HR 1.34; 95% CI: 1.06-1.58), leukocytosis (HR 1.30; 95% CI: 1.06-1.58), anemia (HR 1.28; 95% CI: 1.09-1.49),

and age ≥ 65 years (HR 1.20; 95% CI: 1.02-1.42) were correlated with inferior survival (**Table 5.3**). A test for interaction between ≥1 metastatic sites and surgical resection of the primary tumor was significant (p=0.03), which suggests a larger benefit of surgical intervention in patients with stage IVa disease.

In a secondary analysis, after excluding 116 patients who underwent metastasectomy, primary tumor resection was significantly correlated with better survival (HR 0.43, 95% CI: 0.38-0.51). After adjusting for other important prognostic variables in the Cox proportional multivariate model, the hazard ratio for survival for surgical resection of the primary tumor was 0.52 (95% CI: 0.43-0.65).

5.5 Discussion

Our results suggest that after adjustment of age, performance status, comorbid illnesses and chemotherapy, primary tumor resection in patients with stage IV CRC and asymptomatic or minimally symptomatic primary tumor improves survival. The unadjusted survival difference between the groups with surgery versus no surgery was 11.3 months. The difference was more pronounced among patients who were treated with oxaliplatin- or irinotecan-based chemotherapy, with an absolute survival difference of 13.4 months (29.4 vs. 16 months). Several studies that used registry data have demonstrated survival benefit of resection of the primary tumor in stage IV CRC (2,4,6,7). However, most studies failed to adjust for performance status and other important clinicopathological variables. In agreement with the other reports, our data revealed that patients who underwent surgery were younger with less disease burden compared with the nonsurgical group, which suggests a selection bias for the surgical intervention (2,4). Despite the significance differences between the two groups with respect to age, performance status, albumin, alkaline phosphatase, bilirubin, CEA, sodium, white blood cell count, rectal tumor, tumor grade, number of metastatic sites, use of chemotherapy and mestastasectomy, surgery of the primary tumor resulted in a 53% relative reduction in mortality after adjustment of other variables. To our knowledge, the present study is the only study that controlled for all the important clinical variables to minimize selection bias and has shown survival benefit with resection of the primary tumor.

Our results also revealed a positive interaction between the disease burden, age, CEA level and second-line chemotherapy and resection of the primary tumor. However, in multivariate analysis, after adjustment for the other prognostic variables only the interaction term between resection of the primary tumor and stage IVA disease was significant. Although patients with stage IVa and IVb disease benefited from surgical removal of the primary tumor, the magnitude of benefit was significantly higher in patients with stage IVa disease. Patients with stage IVa disease who received chemotherapy and underwent surgery had median overall survival of 22.4 months (95%CI: 18.5-26.2) versus 12.7 months (95%CI: 7.7-17.6) if they had stage IVb disease. Of note, after excluding 116 patients who underwent metastasectomy, the survival benefit of resection of the primary tumor was maintained independent of other prognostic factors.

A benefit for resection of the primary tumor in stage IV renal cell cancer has been demonstrated in two randomized controlled trials [8,9]. Furthermore, observational studies support resection of the primary tumor in women with metastatic breast cancer (10). The underlying mechanism that results in a better outcome in patients with the removal of the primary tumor remains speculative.

It has been proposed that removal of the primary tumor in advanced colorectal cancer by preventing local tumor complications and reducing the tumor bulk may improve outcome, yet recent reports suggest that in asymptomatic patients with stage IV CRC, leaving the primary tumor intact does not cause unacceptable complications or compromise their survival (3). There is evidence for the genetic variation between the primary tumors and metastases (11). Removal of the primary tumor might result in a decreased burden of chemotactic cytokines and tumor-promoting factors that are produced by CRCs and regulate tumor cells growth and metastasis (12,13). In addition, alteration in immune response following surgery, with predominant T helper 1 (Th1) response than one with a substantial T helper 2 component, might contribute to a better outcome (14).

In this subcohort of asymptomatic or minimally symptomatic patients, in addition to resection of the primary tumor, use of any chemotherapy, metastasectomy, and second-line chemotherapy were correlated with superior survival. Conversely, old age, ECOG performance status of 2 or above, abnormal bilirubin, low albumin, high grade tumor, leukocytosis, and anemia, were associated with inferior survival.

5.6 Conclusions

Our results support survival benefit of resection of rectal or colonic tumor in patients with stage IV CRC and asymptomatic or minimally symptomatic primary tumor independent of age and performance status. The benefit was more pronounced in patients with limited burden of the disease. Two randomized controlled trials in Europe are currently enrolling patients to confirm benefit of surgery (15,16). In the SYNCHRNOUS trial resection of the primary tumor will be compared with no resection in patients with colon cancer and synchronous metastases who are not amenable to curative therapy (15). The CAIRO 4 trial is being conducted to evaluate this question in patients with both stage IV colon and rectal cancer (16). If the magnitude of survival benefits is confirmed in these randomized studies, primary tumor resection could potentially be a more cost-effective intervention compared with novel systemic therapy in the management of metastatic CRC.

5.7 References

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Table 5.1: Characteristics of study cohort and subgroups of patients who underwent surgery versus did not have surgical intervention.

Variables	Total N=834 (100)	Surgery N=521 (62.5)	Control N=313 (37.5)	P value
Demographic (%)				
Median Age (range)	70 (22-93)	69 (22-93)	71 (35-92)	0.001
Age Greater Than 65 yrs	560 (67.1)	330 (63.3)	230 (73.5)	0.003
Comorbid Illness	519 (62.2)	312 (59.9)	207 (66.1)	0.07
ECOG performance status ≥2	215 (25.8)	102 (19.6)	113 (36.1)	<0.001
Male	483 (57.9)	297 (57)	186 (59.4)	0.51
Smoker (Active or Ex-smoker)	380 (45.6)	234 (44.9)	146 (46.6)	0.66
Diagnosed after year>1999	353 (42.2)	191 (36.7)	162 (51.8)	<0.001
Laboratory Value ± (SD)				
Mean Albumin	34.0 ±5.4	34.7±5.6	32.8±4.8	<0.001
Mean Alkaline Phosphtase U/L	201 ±262	183±261	230±262	0.01
Mean Bilirubin umol/l	14±29	12.9±24.2	17.8±35.6	0.02
Mean BUN mmol/l	6.0±4.6	5.9±5.1	6.3±3.7	0.14
Mean CEA ug/l	287.6±1785	181.8±640.5	463.8±2789.6	0.027
Mean Sodium meq/l	138±3.5	138±3.0	137±4.1	0.007
Mean Creatinine umol/l	90.8±33.7	89.6±33.4	92.7±34	0.19
Mean Hemoglobin g/l	118±16.3	117.7±16.3	118.6±16.2	0.40
Mean Platelet 100 x 10^9/l	351±123	347±121	356±125	0.34
Mean WBC 1 x 10^9/l	9.2±4.2	8.9±4.2	9.8±4.1	0.002
Clinco-pathological Features (%)				
Rectal Tumor	273 (32.7)	156 (29.9)	117 (37.4)	0.027
High-grade	150 (18)	105 (20.2)	45 (14.4)	0.04
Liver Metastases	643 (77.1)	400 (76.8)	243 (77.6)	0.79
Extra-hepatic Disease	388 (46.5)	231 (44.3)	157 (50.2)	0.11
More than 1 Metastatic site	231 (27.7)	128 (24.6)	103 (32.9)	0.011
Mucinous Tumor	110 (13.2)	90 (17.3)	20 (6.4)	<0.001
Treatment (%)				
Received Chemotherapy	361 (43.3)	274 (52.6)	87 (27.8)	<0.001
Received Second Line Treatment	135 (16.2)	107 (20.5)	28 (8.9)	<0.001
Received Radiation Therapy	128 (15.3)	80 (15.4)	48 (15.3)	1.0
Second Generation Chemotherapy	158 (18.9)	111 (21.3)	47 (15)	0.028
Metastasectomy	116 (13.9)	107 (20.5)	9 (2.9)	<0.001

BUN=blood urea nitrogen; CEA=carcinoembryonic antigen; ECOG=Eastern Cooperative Oncology Group; SD=standard deviation; WBC= white blood cell count.

Table 5.2: Univariate analysis of factors correlated with survival in patients with stage IV colorectal cancer.

Variables	HR	95% CI	P value
Interventions			
Received any chemotherapy	0.32	0.27-0.37	<0.0001
Surgical Resection of the Primary Tumor	0.38	0.33-0.41	<0.0001
Metastasectomy	0.34	0.27-0.42	<0.0001
Second Line Therapy	0.42	0.35-0.51	<0.0001
Second Generation Therapy	0.45	0.38-0.54	<0.0001
Demographic			
Age ≥65 yrs	1.48	1.27-1.72	<0.0001
Male	1.14	0.99-1.31	0.077
ECOG Performance Status ≥2	2.54	2.16-3.0	<0.0001
Comorbid Illness	1.24	1.08-1.44	0.003
Smoker (active or ex-smoker)	1.09	0.94-1.25	0.23
Time Period (year<2000)	1.04	0.90-1.19	0.63
Laboratory Value			
Alkaline Phosphatase≥ 120 U/L	1.58	1.36-1.85	<0.0001
BUN ≥8 mmol/l	1.23	0.97-1.55	0.078
CEA >5 ug/l	2.51	2.01-3.14	<0.0001
Creatinine ≥120 umol/l	1.31	1.02-1.69	0.036
Sodium <136 meq/l	1.53	1.25-1.87	<0.0001
Bilirubin ≥26 umol/l	2.67	2.02-3.54	<0.0001
Albumin <35 g/l	2.28	1.96-2.65	<0.0001
Hemoglobin <120 g/l	1.45	1.26-1.67	<0.0001
WBC >11 x 10^9/l	1.89	1.57-2.26	<0.0001
Platelets >450 x 10^9/l	1.01	0.83-1.22	0.91
Tumor Characteristics			
Extra-Hepatic Disease	1.06	0.92-1.22	0.40
Grade III Tumor	1.21	1.01-1.45	0.041
Liver Metastases	1.36	1.15-1.61	<0.0001
More than 1 Metastatic Sites (Stage IVB)	1.53	1.31-1.79	<0.0001
Mucinous Cancer	0.83	0.68-1.03	0.085
Colon Cancer	1.21	1.04-1.40	0.012
Significant Interaction Terms			
Age ≥65 * SRPT	1.54	1.12-2.10	0.007
CEA * SRPT	2.06	1.17-3.62	0.012
Moe than 1 metastatic site * SRPT	1.73	1.27-2.37	0.001
Second line therapy * SRPT	0.58	0.37-0.92	0.02

BUN=blood urea nitrogen; CEA=carcinoembryonic antigen; ECOG=Eastern Cooperative Oncology Group; SRPT=surgical resection of primary tumor

Table 5.3: Cox Proportional multivariate analysis of factors correlated with survival in patients with stage IV colorectal cancer.

Variables	HR	95% CI	P value
Received Chemotherapy	0.44	0.36-53	<0.0001
Surgical Resection of the Primary Tumor	0.47	0.39-57	<0.0001
Metastasectomy	0.49	0.38-0.61	<0.0001
Second Line Therapy	0.73	0.58-0.92	0.007
Age ≥65 yrs	1.20	1.02-1.42	.031
Male gender	1.12	0.97-1.30	0.13
ECOG Performance Status ≥2	1.36	1.15-1.62	<0.0001
Comorbid Illness	1.13	0.97-1.31	0.11
Alkaline Phosphatase≥ 120 U/L	1.50	1.26-1.77	<0.0001
Bilirubin ≥26 umol/l	1.48	1.08-2.01	0.014
Albumin <35 g/l	1.48	1.25-1.75	<0.0001
Hemoglobin <120 g/l	1.28	1.10-1.49	0.002
WBC >11 x 10^9/l	1.30	1.06-1.58	0.01
Grade III tumor	1.34	1.11-1.62	0.002
More than 1 Metastatic Sites	0.96	0.76-1.22	0.74
More than 1 Metastatic Sites * surgery of primary tumor	1.43	1.04-1.97	0.03

Figure 5.1: Survival of patients who underwent surgery compared with if they did not have surgery adjusted for chemotherapy (5-FU-based monotherapy) (A) and (B) second-generation chemotherapy (oxaliplatin or irinotecan).

Figure 5.1A

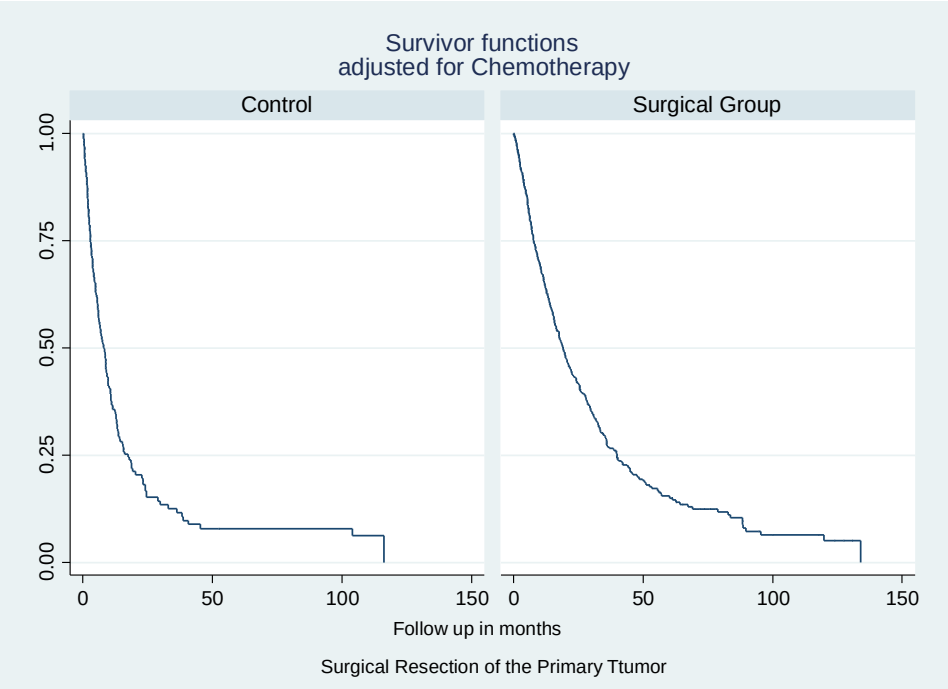
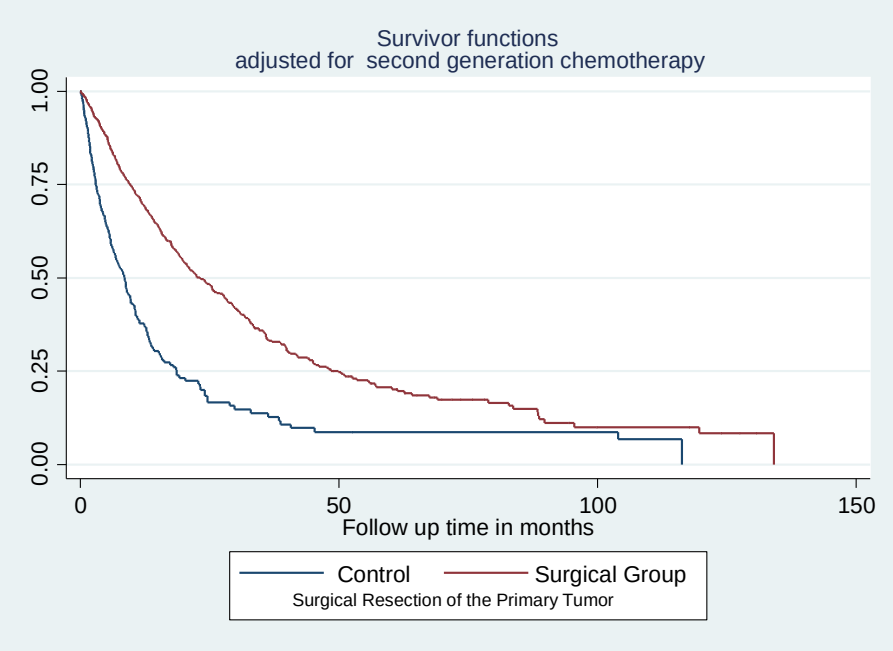


Figure 5.1B



CHAPTER 6– COHORT STUDY (2006-2010): PATIENTS DIAGNOSED DURING THE PERIOD OF MODERN CHEMOTHERAPY

Our research revealed that primary tumor resection improves survival of a cohort of patients with stage IV CRC, who were diagnosed between 1992-2005, independent of other important prognostic variables such as chemotherapy, metastasectomy, comorbid illness, and performance status. Overall primary tumor resection resulted in 46% relative reduction in mortality. However, only 42% of patients were treated with systemic therapy and of treated patients, only about 45% received modern combination chemotherapy regimen. Moreover, less than 5% received a biological agent. It is not known if the benefit of primary tumor resection maintains with the use of more effective systemic therapy. The present study was conducted to validate our findings in a cohort of patients with stage IV CRC who were diagnosed during the period of modern systemic therapy.

This chapter concentrates on the study objective "to determine survival advantage of primary tumor resection in patients with stage IV CRC during the period of modern chemotherapy". The study findings were presented in January 2015 at the Gastrointestinal Cancer Symposium in San Francisco, USA. Notably, our study scored 9 of 9 using the 'validity scoring for observational study' for overall survival, and met the criteria for good quality study (**Appendices F and O**). The result was published in the Journal of Cancer *"Ahmed S, Leis A, Kanthan S, Fields A, Reeder B, Iqbal N, Haider K, Le D, Pahwa P. Surgical management of the primary tumor in Stage IV colorectal cancer: a confirmatory retrospective cohort study. Journal of Cancer. 2016;7(7):837-845.doi:10.7150/jca.14717*

6.1 Abstract

Background: Previous observational studies have suggested that patients with stage IV colorectal cancer who undergo primary tumor resection have better survival. Yet the results are not confirmed in the setting of a randomized controlled trial. Lack of randomization and failure to control prognostic variables such as performance status are major critiques to the findings of the observational studies. We previously showed that primary tumor resection, independent of chemotherapy and performance status, improves survival of stage IV CRC patients. The current study aims to validate our findings in patients with stage IV CRC who were diagnosed during the period of modern chemotherapy.

Methods: A cohort of 569 patients with stage IV CRC diagnosed during 2006-2010 in the province of Saskatchewan was evaluated. Cox regression model was used for the adjustment of prognostic variables.

Results: Median age was 69 years (59-95) and M: F was 1.4:1. Fifty-seven percent received chemotherapy, 91.4% received FOLFIRI or FOLFOX & 67% received a biologic agent. Median overall survival (OS) of patients who underwent primary tumor resection and received chemotherapy was 27 months compared with 14 months of the non-resection group ($p<0.0001$). Median OS of patients who received all active agents and had primary tumor resection was 39 months (95% CI: 25.1-52.9). On multivariate analysis, primary tumor resection, HR: 0.44 (95% CI: 0.35-0.56), use of chemotherapy, HR: 0.33 (95% CI: 0.26-0.43), metastasectomy, HR: 0.43 (95% CI: 0.31-0.58), second-line therapy, HR: 0.50 (95% CI: 0.35-0.70), and third-line therapy, HR: 0.58 (95% CI: 0.41-0.83) were correlated with superior survival.

Conclusions: The present study confirms our findings and supports a favorable association between primary tumor resection and survival in patients with stage IV CRC who are treated with modern therapy.

6.2 Introduction

Several observational studies have demonstrated superior survival of patients with stage IV CRC who undergo primary tumor resection (1-6). For example, a systematic review and meta-analysis of 15 observational studies involving 12456 patients with stage IV CRC demonstrated a hazard ratio (HR) for mortality of 0.69 (95% CI: 0.61-0.79) favoring surgery (2). A subsequent meta-analysis involving 44,226 patients in 21 studies indicated potential benefit of primary tumor resection in patients with unresectable metastases (odd ratio of 0.28; 95 % CI: 0.17-0.47), translating into a difference in mean survival of 6.4 months in favor of resection (3). Yet the results are not confirmed in the setting of a randomized controlled trial. Lack of randomization and failure to control prognostic variables that affect survival including systemic therapy and performance status are major critiques to the findings of the observational studies. Consequently, the survival benefit related to surgery has been attributed to selection bias and selection of younger and healthier patients with good performance status.

Our group has demonstrated that primary tumor resection improves survival of a cohort of patients with stage IV CRC, who were diagnosed between 1992-2005, irrespective of age, comorbid illness, performance status, chemotherapy, metastasectomy and other important prognostic variables (1). In this group of patients primary tumor resection was associated with 46% relative reduction in mortality (HR 0.54, 95%CI: 0.41-0.58). However, only 42% of patients were treated with systemic therapy. Among the treated patients about 45% received irinotecan or oxaliplatin based (FOLFIRI or FOLFOX) chemotherapy. Moreover, less than 5% patients received a biological agent. It is not known if similar benefit can be achieved with the use of more effective chemotherapy and biological agents in the management of metastatic CRC. We have undertaken the current study to confirm our findings in a cohort of patients with stage IV CRC who were diagnosed during the period of modern systemic therapy.

6.3 Objectives

The study objectives were to validate prognostic impact of primary tumor resection in patients with stage IV CRC who were treated with modern systemic therapy and to assess interaction of removal of primary tumor with other prognostic variables in order to identify subgroups of patients who received greater benefit from surgery.

6.4 Methods

6.4.1 Eligibility Criteria

The study protocol was approved by the University of Saskatchewan's Ethics Board. Individual records of patients ≥18 years, diagnosed with synchronous stage IV CRC between 2006 and 2010 in the province of Saskatchewan were reviewed. Patients with previous history of CRC, with another active second primary cancer, or who had pathology other than adenocarcinoma were excluded.

6.4.2 Statistical Analysis

The primary end point of this study was to determine relationship between primary tumor resection and overall survival (OS). Survival was estimated by using the Kaplan-Meier method. Survival distribution of subgroups was compared by the Log Rank test.

Charlson comorbidity index was used in this confirmatory study to defined major comorbid illness (7). A multivariate analysis was performed to determine the prognostic significance of primary tumor resection in patients with stage IV CRC in relation to other clinicopathological variables. The Cox proportional hazard model was used and the hazard ratio and its 95% CI were estimated.

The following variables were examined with respect to their prognostic significance:

Interventions: Resection of the primary tumor, metastasectomy, use of chemotherapy with or without biologics , second line therapy, third line therapy, and radiation therapy; clinical & demographic variables: age (<65 vs. ≥65), gender, major comorbid illness (as per Charlson comorbidity index), secondary cancer, ECOG performance status (<2 vs. ≥2), cancer center, and smoking; laboratory values: albumin (≥36 vs. <36 g/l), bilirubin (≥26 vs. <26 um/l), alkaline phosphatase (≥120 vs. <120 U/l), sodium level (≤135 mEq/l vs. >135 mEq/l), serum creatinine (≥120 vs. <120 um/l), BU) (≥8 vs. <8 mm/l), hemoglobin (≥120 vs. <120 g/l), WBC (≥11 vs. <11 x 10^9/l), platelet count (≥450 vs. <450 x10^9/l), and CEA (≥6 vs. <6 ug/l); disease characteristics: site (colon vs. rectal), grade (Grade 3 vs. <3), symptomatic disease, extra-hepatic metastases, and stage (stage IVa vs. stage IVb disease). For the Cox proportional hazard model, log-log survival curves was used to assess the proportional hazards assumption.

All variables that were significant on univariate analysis with P<0.05, were examined in multivariate models. The likelihood ratio test and the *t* test were used to determine if a variable correlates with survival in the model. A test for interaction was performed for primary tumor resection and the other variables that were correlated with survival. In addition, secondary analyses were performed in subgroups of patients with asymptomatic disease, or patients who did not have metastasectomy. A two-sided P-value of <0.05 was considered to be statistically significant. For missing data imputation technique was used. All patients were followed till June 2014 when the data entry was closed. The SPSS version 22 was used for statistical analysis (SPSS Inc. Chicago, IL).

6.5 Results

6.5.1 Baseline Characteristics

Five hundred and sixty-nine eligible patients with synchronous stage IV CRC were identified (**Figure 6.1**). Their median age was 69 years (range: 59-95) and male: female was 1.4:1. Three hundred and thirteen (55%) patients underwent surgery and 256 (45%) did not have surgery. Of 569 patients, 340 (60%) were ≥65 years and 201 (35%) had ECOG performance status of ≥2 (**Table 6.1**). Although no significant differences were noted between the two groups with respect to age, gender, comorbid illness, and smoking status, 122 (48%) patients in the non-resection group had ECOG performance status of >1 compared with 79 (25%) patients in the resection group ($p<0.001$). In addition, significant differences were noted between the two groups in relationship with serum creatinine, CEA and bilirubin.

6.5.2 Systemic Therapy

Overall 326 (57%) patients received chemotherapy, 199 (64%) in the resection group and 127 (50%) in the non-resection group ($p=0.001$). Of 326 patients, 298 (91%) received either FOLFIRI (infusional 5 fluorouracil, leucovorin and irinotecan) or FOLFOX (infusional 5 fluorouracil, leucovorin and oxaliplatin), 157 (48%) received both FOLFIRI and FOLFOX, 213 (65%) received bevacizumab, and 34 (10%) patients with KRAS wild tumor (about 60% had KRAS wild disease) received cetuximab or panitumumab. Of 326 patients who were treated with chemotherapy, on progression, 174 (53%) received second-line chemotherapy and 52 (16%) received third-line therapy. FOLFIRI in combination with bevacizumab was the preferred first line regimen in most patients who were treated with systemic therapy. On progression, FOLFOX was given as second-line therapy and panitumumab or cetuximab alone or in combination with irinotecan was used as the standard third-line therapy in patients with KRAS wild tumor. There was no significant difference between the two groups in relation to second- and third-line therapies (**Table 6.1**). Furthermore, no significant difference was noted between the two groups with respect to types of systemic therapy, however, 45% patients in the resection group who were treated with systemic therapy received all available therapy (FOLFIRI, FOLFOX and a biologic agent) compared with 35% of patients in the non-resection group ($p=0.045$). Of 199 patients in the resection group who received chemotherapy, 172 (86%) received chemotherapy after surgery. The median time to start chemotherapy was 79 days (IQR: 64-106).

6.5.3 Disease Characteristics

Overall about 41% patients in the non-resection group had rectal or rectosigmoid primary tumor compared with 28% in the resection group ($p=0.001$). In addition, approximately 54% patients in the non-resection group had stage IVb disease compared with 40% in the resection group ($p=0.001$). Patients in the resection group had significantly more often peritoneal disease compared with patients in the non-resection group who had more often lung or bone metastases.

6.5.4 Post-operative Morbidity and Mortality

Median duration of hospital stay of was 9 days (inter-quartile range: 7-13). Of 313 patients who underwent surgery 74 (24%) patients developed post-operative complications. Among 74 patients who developed operative complications 65% had a symptomatic primary tumor. Post-operative complications rates were not mutually exclusive and were as followed: post-operative wound infection in 7% patients, non-wound infection in 5% patients, and anastomotic leak, wound dehiscence, bleeding, and pulmonary embolism in 2% each. Major complications including venous thromboembolism, sepsis, wound dehiscence, anastomotic leakage, post-operative bleeding, pelvic abscess and ischemic bowel were noted in 37 (12%) patients. Of note, 10 (7%) of 142 patients with asymptomatic or minimally symptomatic tumor developed major complications compared with 27 (16%) of 171 patients with symptomatic primary tumor (p=0.01).

Overall the 30-day mortality rate of the group that underwent surgery was 5%. Fifteen of 171 (9%) patients with symptomatic disease compared with 2 (1%) of 142 patients with asymptomatic or minimally symptomatic disease died within 30 days of surgery (p=0.003).

6.5.5 Non-surgical Interventions

Overall 30 (5%) patients required a stent for their symptoms. Eight (3%) of 313 patients who underwent surgery compared with 22 (9%) of 256 patients who did not have surgery required a stent (p=0.001). All eight patients in the surgery group had the stent placed prior to the surgery. In addition, 38 (15%) patients in the non-resection group developed obstructive symptoms and required a stoma formation (colostomy or ileostomy). Forty-five (14%) patients in the resection group compared with 45 (17.6) of 256 patients in the non-resection group received radiation therapy (p=0.30).

6.5.6 Follow-up & Survival

Median follow-up time for the entire cohort was 11 months (inter-quartile range: 2-26 months). No patient was lost to follow-up. Median overall survival of patients who underwent removal of the primary tumor, irrespective of the use of systemic therapy, was 18 months (95% CI: 15.4-20.6) compared with 4 months (95% CI: 2.6-5.4) if they did not have surgery (p<0.001). Median overall survival (OS) of patients who underwent primary tumor resection and received chemotherapy was 27 months (95%CI: 23.3-30.8) versus 14 months (95%CI: 11.2-16.8) if they received chemotherapy but did not have surgery (p<0.001) [**Figure 6.2**]. Patients who received second-line therapy and underwent SRPT had median OS of 30 months (95%CI: 24.9-35.1) compared with 20 months (95%CI: 17.7-22.3) if they did not have surgery (p<0.001) [**Figures 6.3A & 6.3B**]. About 30% patients on progression received third-line therapy. The median OS of patients who received third-line therapy and underwent primary tumor resection was 39 months (95%CI: 22.1-44.9) compared with 26 months (95%CI: 10.3-41.7) if they did not have surgery (p=0.13). Median OS of patients who received FOLFIRI and FOLFOX and a biologic agent (bevacizumab or anti-EGFR monoclonal antibodies) and underwent primary tumor resection was 35 months (95% CI: 30-40) compared with 23 months (95%CI: 19.8-26.3) if they did not surgery (p<0.001) [**Figure 6.4**]. A subgroup of patients with asymptomatic or minimally symptomatic primary tumor who underwent surgery and received systemic therapy had a median OS of 34 months (95%CI: 26.6-43.4)

compared with median OS of 14 months (95%CI: 11.1-17.0) if they did not have surgery (p<0.001).

6.5.7 Cox Proportional Multivariate Modeling for Survival

One univariate analyses several variables were correlated with survival (**Table 6.2**). The tests for interaction were significant between resection of primary tumor and metastasectomy, second line therapy, stage IVb disease and elevated BUN. On multivariate analysis primary tumor resection independently correlated with superior survival with HR for mortality of 0.44 (95% CI: 0.35-0.56). In addition, chemotherapy, HR 0.33 (95%CI: 0.26-0.43), metastasectomy, HR 0.43 (95% CI: 0.31-0.58), second-line therapy, HR 0.50 (95%CI:0.35-0.70), and third-line therapy, HR 0.58 (95% CI:0.41-0.83) were correlated with superior survival whereas elevated alkaline phosphatase, HR 1.50 (95%CI:1.20-1.78), Grade 3 tumor, HR 1.33 (95% CI:1.10-1.62), leukocytosis, HR 1.32 (95% CI:1.05-1.66), stage IVb disease, HR 1.31 (95% CI:1.10-1.56), and ECOG PS >1, HR 1.30 (95% CI:1.04-1.57) were correlated with inferior survival (**Table 6.3**).

After adjustment for other prognostic variables only the interaction between resection of primary tumor and subsequent line of therapy was significant, which suggests a differential benefit of removal of primary tumor in patients who received other line of therapies. Patients who underwent resection of primary tumor and received second-line therapy had a median OS of 30 months (95% CI: 24.9-35.1) compared with 20 months (95% CI: 17.7-22.3) if they did not have surgery (p <0.001). Conversely, patients who had resection of primary tumor but did not receive second-line therapy had a median OS of 19 months (95% CI: 11.8-26.2) compared with 7 months (95% CI: 5.4-8.6) if they did not have surgery (P<0.001).

6.5.8 Secondary Analyses

In the secondary multivariate analyses that excluded the patients who underwent metastasectmy, SRPT was independently associated with significant reduction in mortality with HR, 0.48 (95% CI: 0.38-0.61). Likewise, in a subgroup of 345 patients with asymptomatic or relatively asymptomatic primary tumors, resection of primary tumor was significantly correlated with better survival with HR 0.32 (95% CI: 0.22-0.45). Similar benefits were noted in subcohorts of patients with colon cancer or ECOG performance status of 0 or 1. In the subgroup of 379 patients with colon cancer, surgery independently correlated with survival with HR for mortality of 0.39 (95% CI: 0.29-0.53). After excluding patients with poor performance status, primary tumor resection remained an independent prognostic variables with HR of 0.48 (95% CI: 0.35-0.66).

6.6 Discussion

The present study confirmed the survival benefit of primary tumor resection in patients who were treated with combination chemotherapy and biologics. In addition to surgery of the primary tumor, systemic therapy, subsequent line of therapies, metastasectomy, elevated alkaline phosphatase, Grade 3 tumor, leukocytosis, stage IVb disease, and performance status were correlated with survival. A significantly higher proportion of patients in the non-resection group had low performance status or larger number of metastatic sites involvement. Furthermore, there was imbalance between the two groups in relation to combination therapy and biologics. Nonetheless,

when these variables were included in a multivariate model, primary tumor resection remained an important independent prognostic factor. In fact, the survival benefit was stronger than the other well-established prognostic factors in stage IV CRC including performance status, alkaline phosphatase levels, and the number of metastatic sites (8,9).

The median overall survival of patients with stage IV cancer, who are treated with combination of chemotherapy and biologics in the recent phase 3 clinical trials, has been reported in the range of 24-30 months (10-12). However, our cohort was comprised of real world patients and was inclusive of patients with poor performance status and major comorbid illness. Although the median overall survival of the entire cohort was 11 months (8.8-13.2), the survival of patients who underwent primary tumor resection and received chemotherapy was 27 months (95% CI: 23.3-30.8). Moreover, patients who underwent primary tumor resection and received second- and third-line therapy had median OS of 30 months (95% CI: 24.9-35.1) and 39 months (95% CI: 22.1-44.9), respectively.

Recent literature also supports survival benefit of primary tumor resection in the era of modern chemotherapy. A retrospective analysis of CAIRO study that compared combination versus sequential chemotherapy demonstrated a significantly better median OS of 16.7 months in patients who underwent primary tumor resection compared with 11.4 months with no surgery (HR 0.61, 95% CI:49–0.76) [6]. Likewise, a pool analysis of four French phase 3 trials involving 850 patients indicated survival benefit of surgery (4). More than two third of patients were treated with FOLFIRI or FOLFOX and about 12% received bevacizumab. The primary tumor resection was an independent predictor of superior survival (HR: 0.63, 95% CI: 0.53-0.75). In addition, our group' meta-analysis of fifteen observational studies did not reveal a positive interaction between surgery and type of chemotherapy.

In agreement with previous observation, patients with asymptomatic or minimally symptomatic disease following surgery had longer survival compared with patients with symptomatic primary tumor (13). Of note, patients with symptomatic primary tumor had 30-day postoperative mortality rates of 8.8% compared 1.5 % if they had an elective surgery. Emergency surgery has consistently been demonstrated to be an important risk factor for inferior outcome in colorectal surgery (14). We believe that in addition to the biology of symptomatic disease, the 30-day mortality rates most likely accounted for the differences in survival between the two groups. In consistent with our previous observation, significantly higher number of patients with colon tumor underwent surgery compared with patients with rectal cancer. However, compared with the 1992-2005 cohort, patients with rectal cancer did not have better prognosis.

Among the prognostic factors, systemic therapy was the most important prognostic variables. It is known that survival of patients with stage IV CRC is better if they are exposed to all available active therapeutic agents during the course of their disease (15). The subgroup of patients who received combination chemotherapy with bevacizumab and underwent surgery had median survival of 35 months (95% CI: 30-40) whereas patients with KRAS wild tumor who received FOLFIRI & FOLFOX in combination with bevacizumab and subsequently were treated with an anti-EGFR monoclonal antibody had a median OS of 39 months (95% CI: 25.1-52.9).

Due to presence of multicollinearity between various lines of chemotherapy and the type of regimens, these variables were not fitted together in the final model. A secondary analysis using chemotherapy regimens and biological agents as opposed to the subsequent lines of therapies was performed (not reported). Both combination of chemotherapy (HR: 0.67, 95% CI: 0.52-0.87) and biological agents (HR:0.60, 95% CI:0.45-0.78) were independently correlated with superior survival. Of significant importance, when various chemotherapy regimens were fitted in the multivariate model, resection of primary tumor was independently correlated with survival.

Our study revealed positive interaction between primary tumor resection and second-line therapy. The patients who had surgery and received second-line therapy had a median OS of 30 months compared with 19 months if they did not receive second-line therapy (p=0.005). With access to novel agents and their efficacy in the primary tumor as well as lack of major complications related to an intact primary tumor, primary tumor resection is less commonly performed (16-18). Our results, however, support potential benefit of surgery in patients who are treated with modern chemotherapy and suggest a greater benefit in patients who are treated with subsequent line of therapy. Our study is unique that it included performance status, an important prognostic variables in metastatic CRC, in the multivariate model. Most population based studies that support benefit of surgery lack individual patients' data and have failed to include performance status in the multivariate models.

In summary, the current study suggests survival benefit of primary tumor resection in patients with advanced CRC. To date, no randomized trial has reported survival impact of primary tumor resection in stage IV CRC. Only a prospective randomized trial could confirm the survival benefit conferred by the primary tumor resection. Such trials are ongoing in Europe and will be important to solve this very important question in the management of stage IV CRC.

6.7 References

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Table 6.1: Characteristics of patients in the entire cohort and subgroups of patients who were treated with surgery and systemic therapy versus systemic therapy alone.

Variables	Study cohort N=569	Resection group N=313 (55)	Non-resection group N=256 (45)	P value
Demographic				
Median age	69 (30-95)	68 (33-95)	70 (30-95)	0.23
Age 65 years or greater	340 (60)	180 (58)	160 (62)	0.23
Previous History of Cancer	82 (14)	39 (13)	43 (17)	0.15
ECOG performance status 2 or more	201 (35)	79 (25)	122 (48)	<0.001
Charlson comorbidity index *	141 (25)	85 (27)	56 (22)	0.056
Male	335 (59)	181 (58)	154 (60)	0.61
Current or ex-smoker	344 (60)	196 (63)	148 (58)	0.26
Laboratory values				
Albumin g/l	32 ±6	33 ±7	31 ±6	0.39
Alkaline phosphatase U/l	202 ±277	179 ±309	230 ±229	0.12
Bilirubin ug/l	15 ±24	11 ±11	18 ±34	<0.001
Blood urea nitrogen mm/l	7 ±27	7 ±29	8 ±24	0.86
CEA ug/l	581 ±3006	376 ±1988	830 ±3895	0.004
Creatinine um/l	91 ±63	86 ±31	97 ±88	<0.001
Hemoglobin g/l	111 ±119	123 ±16	118 ±17	0.82
Platelet 10^9/l	350 ±124	334 ±114	368 ±135	0.061
White blood cell count 10^9/l	11.3 ±47	8.9 ±8	10.2 ±4	0.61
Sodium meq/l	137 ±3	138 ±3	137 ±3	0.27
Treatment				
Chemotherapy	326 (57)	199 (64)	127 (50)	0.001
Second line therapy	174 (53)	110 (55)	64 (50)	0.23
Third line therapy	52 (16)	36 (18)	16 (13)	0.12
FOLFIRI OR FOLFOX	298 (91)	182 (92)	116 (91)	0.56
Biologics	218 (67)	137 (69)	81 (64)	0.24
FOLFIRI & FOLFOX plus a biologics	133 (41)	89 (45)	44 (35)	0.045
Radiation therapy	90 (16)	45 (14)	45 (18)	0.30
Metastasectomy	89 (16)	81 (26)	8 (3)	<0.001
Metastatic sites				
Extra-hepatic disease	305 (54)	151 (48)	154 (60)	0.005
Bone	21 (7)	6 (4)	15 (10)	0.038
Brain	5 (2)	2 (1)	3 (2)	0.50
Lung	125 (41)	50 (33)	75 (49)	0.004
Peritoneum	124 (41)	73 (48)	51 (33)	0.005
Tumor				
Stage IVb	264 (46)	126 (40)	138 (54)	0.001
Grade 3	151 (27)	79 (25)	72 (28)	0.44
Mucinous	55 (10)	39 (13)	16 (6)	0.015
Rectum or rectosigmoid tumor	190 (33)	86 (28)	104 (41)	0.001
Symptomatic primary tumor	224 (39)	171 (55)	53 (21)	<0.001

*Mean Chalrson comorbidity score 9.58±1.53 in resection group compared with 9.50±1.44 non-resection group. Biologics= cetuximab, panitumumab or bevacizumab; CEA= carcinoembryonic antigen; ECOG= Eastern Cooporative Oncology Group; FOLFIRI=Infusional 5-FU, leucovorin and irinotecan; FOLFOX=Infusional 5-FU, leucovorin and oxaliplatin;

Table 6.2: Relationship between various clinicopathological variables and survival in univariate analysis.

Variables	HR (95% CI)	P value	HR (95% CI) for Interaction with SPRT	P value
Age ≥65 years	1.87 (1.56-2.25)	<0.001	1.36 (0.95-1.94)	0.096
Male gender	0.90 (0.75-1.10)	0.22	1.17 (0.83-1.67)	0.37
ECOG PS	2.51 (2.09-3.02)	<0.001	0.94 (0.65-1.36)	0.75
Comorbid illness	1.50 (1.23-1.85)	<0.001	1.11 (0.74-1.67)	0.63
Current Smoking	0.86 (0.69-1.08)	0.20	0.80 (0.52-1.26)	0.35
Ex-Smoking	0.91 (0.76-1.09)	0.31	1 (0.70-1.43)	0.98
Treatment Centers	1.04 (0.87-1.23)	0.68	1.33 (0.94-1.89)	0.11
Albumin <35 g/l	1.95 (1.60-2.39)	<0.001	0.76 (0.49-1.19)	0.23
Alkaline phosphatase >120 U/l	2.17 (1.79-2.62)	<0.001	1.04 (0.70-1.55)	0.85
Bilirubin ≥26 um/l	1.77 (1.28-2.46)	0.001	1.93 (0.97-3.87	0.06
BUN ≥8 mm/l	1.48 (1.13-1.93)	0.007	1.82 (1.05-3.16)	0.034
CEA ≥5 ug/l	2.11 (1.63-2.76)	<0.001	1.18 (0.64-2.20)	0.60
Creatinine ≥120 um/l	1.46 (1.06-1.99)	0.026	1.36 (0.72-2.57)	0.34
Hemoglobin <120 g/l	1.82 (1.49-2.22)	<0.001	0.90 (0.60-1.34)	0.60
Platelet count, ≥450 x10^9/l	0.92 (0.73-1.17)	0.51	1.14 (0.70-1.86)	0.60
WBC ≥11 x 10^9/l	1.39 (1.12-1.71)	0.004	1.30 (0.84-2.01)	0.23
Sodium <135 meq/l	1.19 (0.95-1.48)	0.14	1.02 (0.65-1.60)	0.92
Extra-hepatic disease	1.21 (1.02-1.44)	0.031	1.36 (0.96-1.94)	0.08
Grade 3	1.48 (1.22-1.79)	<0.001	1.34 (0.91-1.97)	0.14
Mucinous pathology	1.13 (0.85-1.51)	0.40	1.74 (0.92-3.28)	0.09
Rectum	0.80 (0.66-0.96)	0.014	0.84 (0.58-1.24)	0.39
Stage IVb disease	1.38 (1.16-1.64)	<0.001	1.43 (1.01-2.03)	0.04
Symptomatic primary tumor	1.08 (0.90-1.28)	0.42	1.05 (0.71-1.55)	0.82
Primary tumor resection	0.44 (0.37-0.53)	<0.001	NA	NA
Metastasectomy	0.30 (0.22-0.40)	<0.001	0.74 (0.58-0.94)	0.015
Chemotherapy	0.24 (0.20-0.29)	<0.001	1.36 (0.95-1.94)	0.09
Second line Treatment	0.44 (0.36-0.53)	0.025	2.10 (1.28-3.35)	0.003
Third line Treatment	0.41 (0.30-0.56)	<0.001	1.77 (0.89-3.49)	0.10
FOLFOX or FOLFIRI	0.27 (0.23-0.33)	<0.001	1.49 (1.04-2.12)	0.029
Biologics	0.34 (0.28-0.41)	<0.001	1.44 (1.0-2.08)	0.05
Radiation	0.66 (0.52-0.84)	<0.001	0.97 (0.60-1.57)	0.90

Biologics= cetuximab, panitumumab or bevacizumab; CEA= carcinoembryonic antigen; ECOG PS= Eastern Cooporative Oncology Group performance status; FOLFIRI=Infusional 5-FU, leucovorin and irinotecan; FOLFOX=Infusional 5-FU, leucovorin and oxaliplatin;

Table 6.3: Relationship between various clinicopathological variables and survival in multivariate analysis.

Variables	HR (95% CI)
Primary tumor resection	
Yes	0.44 (0.35-0.56)
No	1
Chemotherapy	
Yes	0.33 (0.26-0.43)
No	1
Metastasectomy	
Yes	0.43 (0.31-0.58)
No	1
Second line therapy	
Yes	0.50 (0.35-0.70)
No	1
Third line therapy	
Yes	0.58 (0.41-0.83)
No	1
Alkaline phosphatase >120 U/l	
Yes	1.50 (1.20-1.78)
No	1
Grade 3 tumors	
Yes	1.33 (1.10-1.62)
No	1
Leukocytosis	
Yes	1.32 (1.05-1.66)
No	1
Stage IVb disease	
Yes	1.31 (1.10-1.56)
No	
ECOG performance status >1	
Yes	1.30 (1.04-1.57)
No	1

Figure 6.1: Flow diagram of eligible patients with stage IV colorectal cancer patients who underwent surgical resection of primary tumor or did not have surgery.

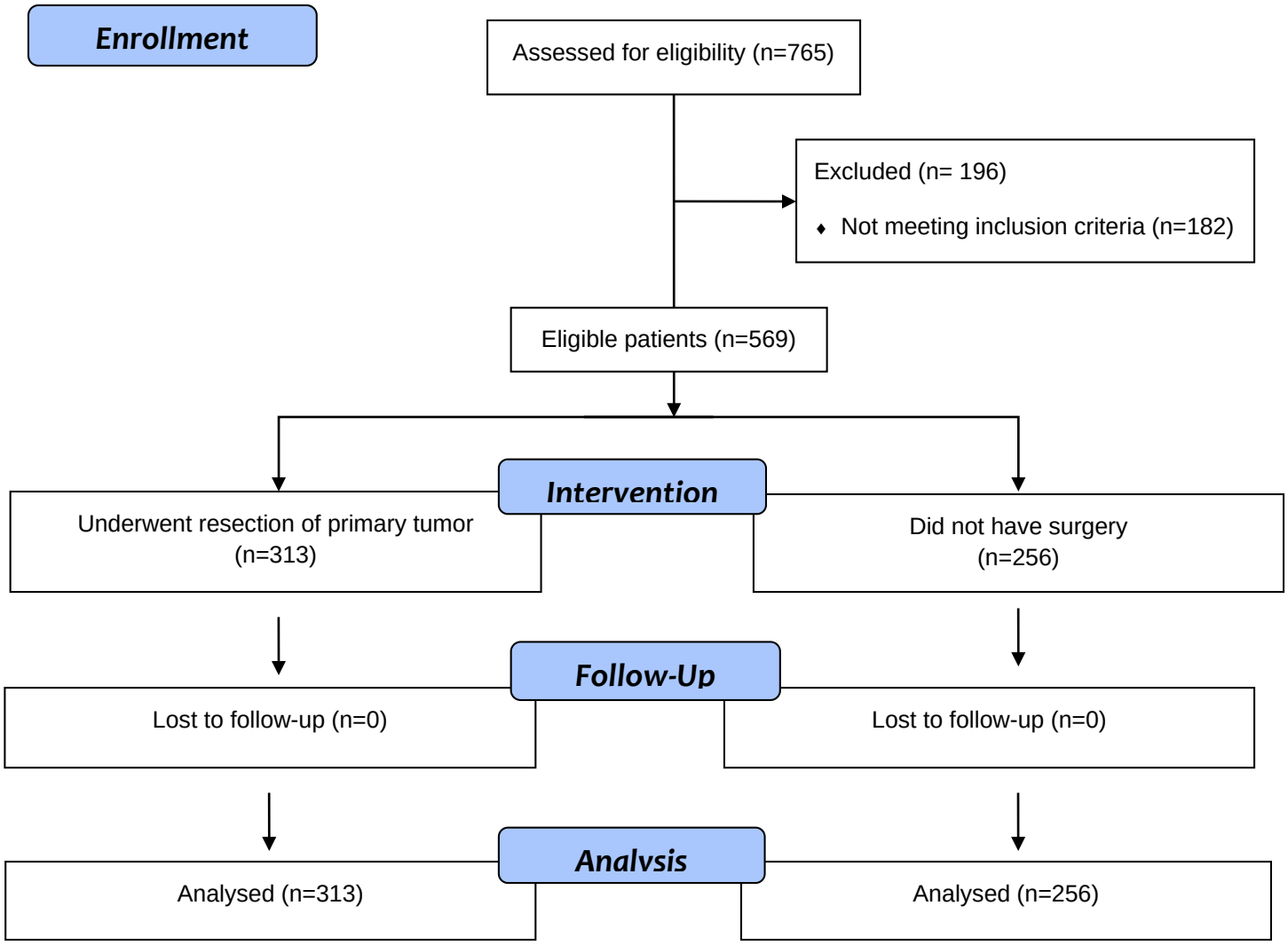


Figure 6.2: Overall survival of patients who underwent surgery compared with no surgical intervention during the period of modern chemotherapy.

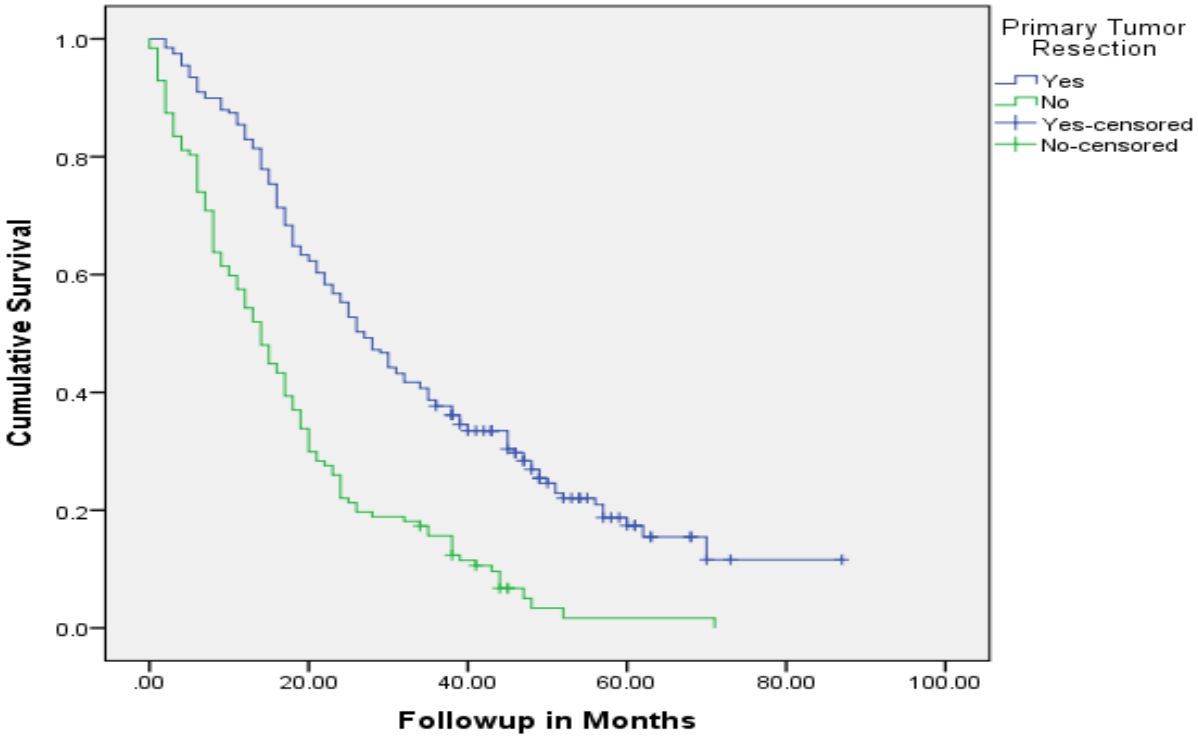


Figure 6.3: Overall survival of patients who received second-line therapy and underwent surgery of the primary tumor (6.3A) versus if they did not receive second-line therapy (6.3B).

Figure 6.3A

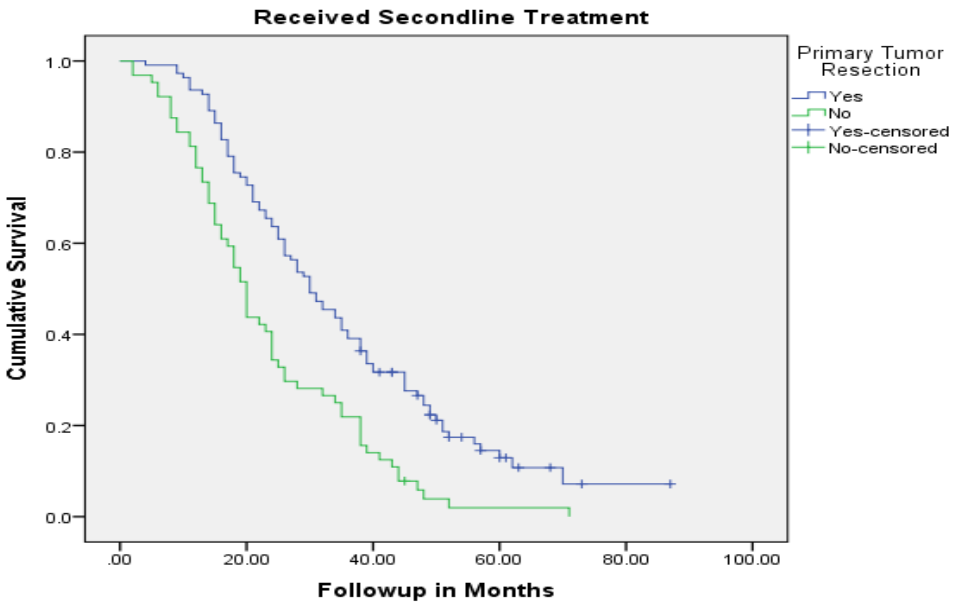


Figure 6.3B

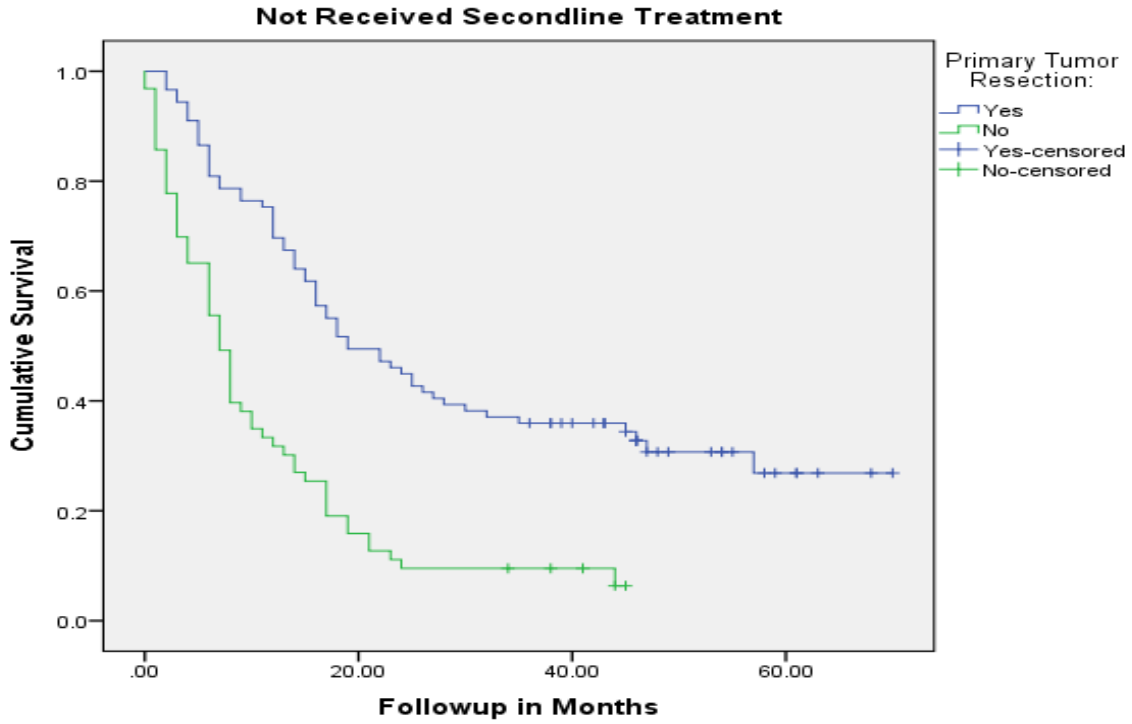
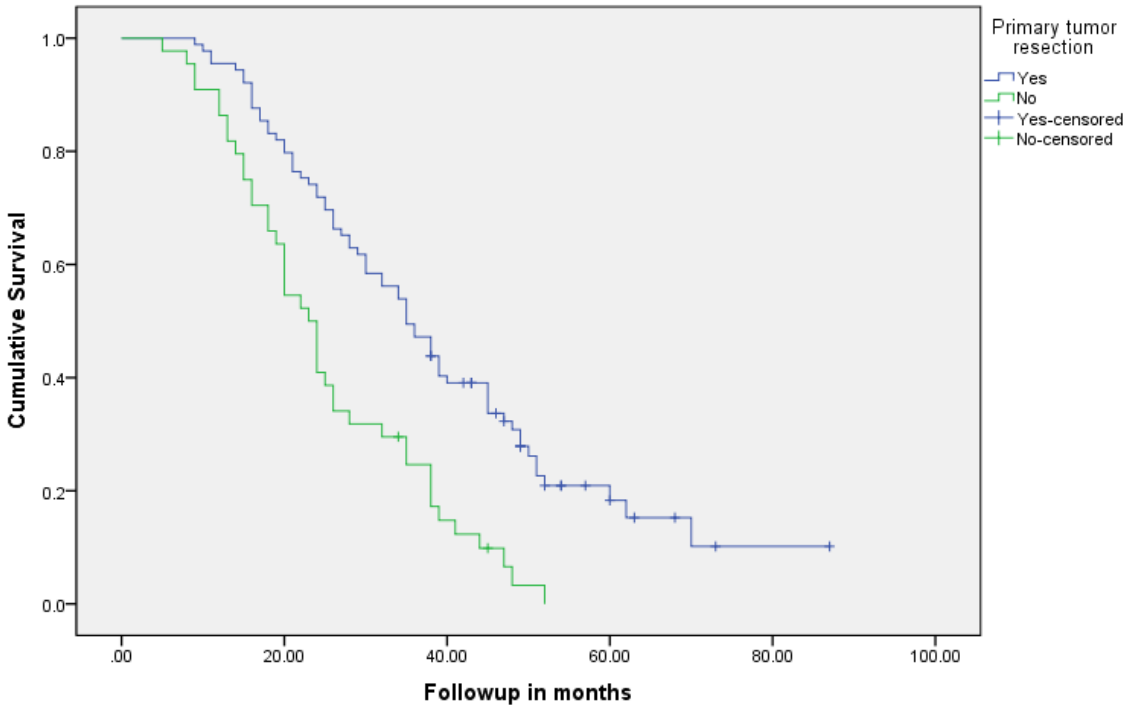


Figure 6.4: Overall survival of patients with stage IV colorectal cancer who were treated with combination of chemotherapy and biologics and underwent surgery compared with no surgery.



CHAPTER 7 – CAMPANION STUDY I: PREDICTIVE FACTORS FOR THE USE OF CHEMOTHERPAY IN METASTATIC COLORECTAL CANCER

The following two chapters will review the results of the two companion studies that are related to our primary research objectives. The present chapter will evaluate the prevalence of the use of chemotherapy in patients with stage IV CRC and its relationship with various variables. The next chapter will assess the prognostic importance of the primary tumor-related factors including regional lymph nodes status and the ratio of metastatic to examined lymph node in metastatic CRC.

Over the past decade combination chemotherapy and biologics have significantly improved the prognosis of patients with stage IV CRC. The aims of chemotherapy in patients with advanced CRC are to prolong survival, to control cancer-related symptoms, and to maintain or improve quality of life. In our 1992-2005 cohort study, chemotherapy was found to be the most important prognostic variable. In a multivariate analysis, after adjustments for other prognostic variables, 5FU-based chemotherapy was associated with 57% relative reduction in mortality (HR for mortality 0.43, 95% CI: 0.36-0.53). The findings were confirmed in the second cohort (2006-2010). For example, use of modern chemotherapy was associated with 67% relative reduction in mortality compared with no chemotherapy (HR 33; 95% CI: 0.26-0.43). Notably, in the 1992-2005 cohort, less than 50% patients received chemotherapy. In general, patients' medical condition is the prime consideration in making a treatment recommendation. Although in a clinical trial setting strict eligibility criteria are used for utilization of chemotherapy, little is known about the use of chemotherapy in general population and whether its utilization is truly guided by patient medical conditions.

The present chapter examines various patients- and tumor-related characteristics and co-interventions that are associated with the use of chemotherapy in patients with stage IV colorectal cancer. Part of the data was presented in June 2011 at the American Society of Clinical Oncology annual meeting in Chicago, USA. The result was published in the Oncology *"Ahmed S, Pahwa P, Fields A, Chandra-Kanthan S, Iqbal N, Zaidi A, Reeder B, Plaza FA, Zhu T, Leis A. Predictive Factors of the Use of Systemic Therapy in Stage IV Colorectal Cancer: Who Gets Chemotherapy? Oncology. 2015;88(5):289-97"*.

7.1 Abstract

Background: Chemotherapy improves survival in patients with stage IV CRC. Although in a clinical trial setting, strict eligibility criteria are used for chemotherapy, little is known about the use of chemotherapy in the general population. The study aims to assess clinicopathological variables that correlate with the use of chemotherapy in patients with stage IV CRC.

Methods: A retrospective cohort study involving patients with stage IV CRC, diagnosed between 1992 and 2005, in the province of Saskatchewan was carried out. A logistic regression analysis was performed to assess correlation of various clinicopathological factors with the use of chemotherapy.

Results: A total of 1,237 eligible patients were identified. Their median age was 70 years (range: 22-98) and M: F ratio was 1.3:1. 23.8% had an ECOG performance status (PS) of ≥2 and 61.8% patients had a comorbid illness. 46.8% patients received chemotherapy. The multivariate logistic regression analysis revealed that age <65 year (OR 3.82, 95% CI: 2.59-5.63), metastasectomy (OR 3.60, 95% CI:1.82-7.10), normal albumin (OR 3.26, 95% CI:2.44-4.36), no comorbid illness (OR 2.87, 95% CI:1.34-6.16), ECOG PS of <2 (OR 2.72, 95% CI:1.94-3.82), normal blood urea nitrogen (OR 2.24, 95% CI:1.40-3.59), palliative radiation (OR 2.03, 95% CI:1.38-2.99), primary tumor resection (OR 2.00, 95% CI:1.47-2.73), and the time period (OR 1.85, 95% CI:1.41-2.42) were significantly correlated with the use of chemotherapy.

Conclusions: The use of chemotherapy appears to be increasing in stage IV CRC. Patients treated with curative intention or who underwent primary tumor resection were more likely to receive chemotherapy. Despite a known benefit of chemotherapy in elderly patients, a differential use of chemotherapy was noted in this population.

7.2 Introduction

Colorectal cancer is the second leading cause of cancer-related death in North America. It is expected to cause more than 50,000 deaths during year 2014 (1). Despite the advent of colorectal cancer screening program approximately 20-30% patients with CRC are diagnosed with stage IV disease. The median overall survival of patients with stage IV CRC with best supportive care alone is about 5-6 months (2). The introduction of novel therapies including two cytotoxic agents, irinotecan and oxaliplatin, and three monoclonal antibodies, bevacizumab, cetuximab and panitumumab, has significantly improved the prognosis of patients with stage IV CRC. Overall, with the judicious use of active agents in the management of CRC, the median overall survival of patients with stage IV CRC has approached to about 30 months (3-6).

Palliative chemotherapy is now offered to an increasing proportion of patients with stage IV CRC. Several groups have published guidelines on the management of advanced CRC (7-9). All groups endorse the use of chemotherapy in stage IV CRC. The aims of chemotherapy in patients with advanced CRC are to prolong survival, control symptoms, and to maintain or improve quality of life. Hence, potential morbidity of treatment and the impact of treatment on patients' quality of life must be considered. The patients' general medical condition is the prime consideration when making a treatment recommendation. In a clinical trial setting, strict eligibility criteria are used for chemotherapy. However, little is known about the use of chemotherapy in the general population and whether its use is truly guided by patients' medical conditions. We conducted a cohort study to assess prognostic significance of the resection of primary tumor in patients with stage IV CRC and noted that less than 50% of patients received chemotherapy (10). The current study aims to assess prevalence of the use of chemotherapy in patients with stage IV CRC and to examine various patients- and tumor-related characteristics and cointerventions that are associated with the use of chemotherapy in patients with stage IV colorectal cancer.

7.3 Methods

7.3.1 Study Population

The study protocol was approved by the Research Ethics Board of the University of Saskatchewan. The study population was comprised of a cohort of consecutive adult patients with histologically documented stage IV adenocarcinoma of colon and rectum, diagnosed in the period of 1992 and 2005, in the province of Saskatchewan, Canada. Patients with other histological diagnosis or with other active secondary malignancy were excluded. In addition, patients who died within 30 days of diagnosis of the cancer were excluded. The Saskatchewan Cancer Registry was used to identify eligible patients. In addition to registry data, individual patients' medical records were retrospectively reviewed. All information was abstracted by a trained research associate using a validated abstraction sheet.

7.3.2 Definitions

The symptomatic primary tumor was defined as the presence of obstruction, perforation or major bleeding. Major comorbid illnesses were defined as the presence of coronary artery disease, diabetes mellitus, chronic renal insufficiency, chronic obstructive lung disease and others (uncontrolled hypertension, peripheral vascular disease, stroke or transient ischemic attack, interstitial lung disease, congestive heart failure, and cardiac arrhythmia). Performance status information was collected using the ECOG scale. If the Karnofsky performance status scale was used, it was converted to ECOG score (11). If performance status was not documented, information was captured by reviewing the consultation notes using a validated abstraction sheet.

7.3.3 Statistical Analysis

The baseline characteristics of patients were compared using the *chi square* and *Student t* test. The cumulative survival rate was calculated using the Kaplan-Meier method, and differences between survival curves were tested with the log-rank test. A multivariate analysis was performed to determine the factors correlated with the use of chemotherapy in patients with stage IV CRC. A logistic regression analysis was done and the odd ratio (OR) and its 95% CI were estimated. The following variables were examined with respect to their correlation with the use of chemotherapy: Age (<65 vs. ≥65), sex, major comorbid illness, ECOG performance status (<2 vs. ≥2), smoking, sodium level (≤135 mEq/l vs. >135 mEq/l), serum creatinine (≥120 vs. <120 um/l), blood urea nitrogen (BUN) (≥8 vs. <8 mm/l), albumin (≥35 vs. <35 g/l), bilirubin (≥26 vs. <26 um/l), alkaline phosphatase (≥100 vs. <100 U/l), hemoglobin (≥120 vs. <120 g/l), WBC (≥11 vs. <11 x 10^9/l), metastatic sites (≥2 or <2), symptomatic primary tumor, extrahepatic metastases, radiation therapy, resection of primary tumor, metastasectomy, and time period (≥ year 2000 vs. <2000). The study cutoff was chosen due to the fact that in the early 1990s, 5-fluorouracil became available for patients with advanced CRC and in the year 2000, irinotecan and subsequently oxaliplatin and monoclonal antibodies became available in the province of Saskatchewan. Tests for interaction were performed for age, performance status, comorbid illness and the other variables.

A two-sided P-value of <0.05 were considered to be statistically significant. All variables that were significant on univariate analysis were subsequently examined in a multivariate model, to assess their correlation with the use of chemotherapy. The likelihood ratio test and *t* test were used to determine whether the addition of independent variables of interest add significantly to the association with the use of chemotherapy in the model. The imputation technique was used for missing data. SPSS version 20 & 21.0 were used for statistical analysis (SPSS Inc. Chicago, IL).

7.5 Results

7.5.1 Patients' Characteristics

Fifteen hundred twenty-nine patients with newly diagnosed stage IV colorectal cancer were assessed for their eligibility. Of those 151 patients were excluded; 114 did not meet the inclusion criteria and 37 had limited medical information. Of remaing1378 patients, 141 were died within 30 days of diagnosis and were excluded from the analysis. A total of 1,237 eligible patients were identified. Their median age was 70 years (range: 22-98) and male to female ratio was 1.3:1. Seven hundred eighty-one (56.8%) patients were male, 294 (23.8%) had ECOG performance status of 2 or greater and 764 (61.8%) patients had a comorbid illness. Of the 1,237 patients, 580 (46.8%) received palliative chemotherapy. Among the patients who received chemotherapy, 263 (45.3%) received irinotecan- or oxaliplation-based combination chemotherapy during the course of their disease. Less than 5% patients were treated with biologics. Of the 263 patients who were treated with novel agents, 218 (83%) received this treatment after the year 1999. The patients' characteristics are described in **Table 7.1**. Significance differences were noted between the two groups with respect to their age, performance status, presence of a comorbid illness, mean serum albumin level, serum bilirubin level, serum creatinine, BUN, CEA, hemoglobin, and presence of leukocytosis. In addition, a significantly higher proportion of patients in the chemotherapy group underwent surgical resection of primary tumor or metastasectomy and received palliative radiation therapy. Three hundred (36.9%) of 812 patients who were ≥65 years of age received palliative chemotherapy compared with 280 (65.9%) of 425 patients who were <65 year (<0.001). Of the 580 patients who received chemotherapy, on progression 83 (37.4%) of the 300 patients ≥65 years of age received second-line therapy compared with 139 (62.6%) of the 280 patients <65 year (<0.001). During the year 2000 and onward, 292 (51.9%) of the 553 patients with advanced CRC received chemotherapy compared with 288 (42.7%) of the 674 patients who were diagnosed before the year 2000 (P<0.001) **(Figure 7.1**). The use of chemotherapy increased with the availability of second-line therapy, but decreased with increasing age at the diagnosis (**Figure 2**).

7.5.2 Multivariate Analysis

On univariate logistic analysis, various clinicopathological factors were identified that were correlated with use of chemotherapy (**Table 7.2**). Among them ECOG performance status of <2, age <65 years, normal albumin, metastasectomy, surgical resection of primary tumor, palliative radiation therapy, and time period were most strongly correlated with the use of chemotherapy. Tests for interaction were significant between age and elevated alkaline phosphatase, metastasectomy, elevated BUN, anemia, extrahepatic disease, male sex, and high grade-tumor, and comorbid illness and metastasectomy. All the significant variables were fitted into a

multivariate logistic regression model. The multivariate logistic regression analysis revealed that age <65 year (OR 3.82, 95% CI:2.59-5.63), metastasectomy (OR 3.60, 95% CI:1.82-7.10), normal albumin (OR 3.26, 95% CI:2.44-4.36), absence of a comorbid illness (OR 2.87, 95% CI:1.34-6.16), ECOG PS of <2 (OR 2.72, 95% CI:1.94-3.82), normal blood urea nitrogen (OR 2.24, 95% CI:1.40-3.59), palliative radiation therapy (OR 2.03, 95% CI:1.38-2.99), primary tumor resection (OR 2.00, 95% CI:1.47-2.73), and the time period (OR 1.85, 95% CI:1.41-2.42) were most strongly correlated with the use of chemotherapy in patients with newly diagnosed stage IV CRC (**Table 7.3**).

7.5.3 Survival

Median time to initiation of chemotherapy from the date of diagnosis was 70 days (interquartile range: 46-107 days). The median follow-up period was 8.8 months (interquartile range: 3.7-19.1). Median survival of the whole cohort was 8.8 months (95% CI: 8.0-9.6) [**Figure 7.3**]. Patients who were treated with chemotherapy had median survival of 16 months (95% CI: 14.6-17.5) compared with 4.6 months (95% CI: 4.1-5.1) if they did not receive chemotherapy (p<0.001). Patients who were diagnosed after the year 1999 and received chemotherapy had a median survival of 17.5 months (95% CI: 15.2-19.9) compared with 14.8 months (95% CI: 13.3-16.3) if they were diagnosed before the year 2000 (P=0.15). With respect to age, patients ≥65 years of age who received chemotherapy had median survival of 15.1 months (95%CI: 13.6-16.6) compared with 17.5 months (95% CI: 15.1-20.0) of patients who were <65 years of age (p=0.01) [**Figure 7.3**]. With respect to performance status, patients with ECOG PS ≥2 who received chemotherapy had median overall survival of 7.6 months (95% CI: 4.0-11.2) compared with a survival of 17.3 months (95% CI: 15.8-18.9) if they have ECOG PS of <2 (P<0.001).

7.6 Discussion

The current study is the first large population-based cohort study, over a time span of fourteen years that assessed the use of chemotherapy in patients with stage IV CRC. Overall, 47% patients were treated with chemotherapy. However, with the availability of novel chemotherapeutic agents in the management of advanced CRC, the prevalence of use of chemotherapy increased from approximately 43 to 52%.

The current study revealed that age, resection of metastatic lesions, normal serum albumin, good performance status, and lack of comorbid illness were most strongly correlated with the use of chemotherapy in patients with newly diagnosed advanced CRC. While the decision to commence chemotherapy is a complex one that must be made on individual basis, our results revealed that independent of comorbid illness, the use of chemotherapy progressively declined with increasing age. Patients of ≥65 years of age were about four times more likely to receive no treatment than younger patients. Moreover, the positive interaction between age and hemoglobin suggests that elderly patients with normal hemoglobin are more likely to receive chemotherapy than patients with anemia. Of note, the majority of colorectal cancers are diagnosed in the elderly population. Moreover, the median age of the study cohort was 70 years. Although few chemotherapy studies in CRC have been specifically designed for elderly patients, there is evidence that elderly patients with good performance status tolerate palliative chemotherapy as well as younger patients and

have similar benefits from palliative chemotherapy (12,13). In the current study elderly patients who received chemotherapy had median survival of 15 months compared with approximately 5 months with best supportive care. There are several clinician- and patient-related factors that may influence the use of chemotherapy in the elderly population. For instance, the oncologist's decision regarding chemotherapy for elderly patients is likely to be based on estimated risk versus benefit. The physiological changes of ageing, presence of comorbid illnesses, and polypharmacy are the key factors that particularly amplify complications of chemotherapy in elderly patients. Conversely, older patients may have different perspective than younger patients when deciding whether to accept chemotherapy, and short-term quality of life may be more important than a modest survival advantage. Furthermore, nonmedical barriers to care such as absence of supportive caregivers may contribute to differential use of chemotherapy in elderly patients.

Our data also demonstrate a strong association between serum albumin and the use of chemotherapy in advanced CRC. Serum albumin provides a simple method of estimating visceral protein function. Malnutrition and inflammation suppress albumin synthesis (14). Low serum albumin is one of the surrogate markers of malnutrition in patients with advanced cancer. Several observational studies have suggested that low serum albumin is associated with higher mortality from cancer (14). Malnutrition in patients with advanced cancer is not uncommon and results from underlying cancer, the host response to the cancer, and anticancer therapies. It has been associated with an increased risk of chemotherapy-related toxicity as well as decreased response to treatment, poor quality of life, and an inferior survival (14,15).

With few exceptions, in most advanced solid tumors, poor performance status correlates closely with reduced survival and in many cases reduced response to chemotherapy (16). Hence, there is a belief that patients with advanced solid tumors with a poor performance status would gain little benefit from chemotherapy. Data on patients with advanced CRC and a poor performance status are scant. Clinical trials often excluded patients with ECOG performance status of ≥ 2 or with a limited life expectancy. In our study cohort, patients with poor performance status, who received chemotherapy had median overall survival of 7.5 months compared with 17 months if they had a good performance status. The modification in the chemotherapeutic regimen and dose reduction may reduce major complications in patients with borderline performance status. In addition, treatment should be started as soon as possible before the performance status further deteriorates. It is not known if access to more effective anticancer therapy, better antiemetics, and growth factors support improve outcomes of such patients.

Of note, for reasons which are not well understood, elevated BUN was inversely correlated with the use of chemotherapy. Elevated BUN, also known as azotemia, is a marker of dehydration and gastrointestinal bleeding. It has been identified as a poor prognostic variable in patients with advanced cancer and correlates with seven days' mortality (17). Furthermore, a negative correlation was noted between comorbid illness and use of chemotherapy. Ageing is associated with a high prevalence of comorbid diseases including hypertension, coronary artery disease, diabetes mellitus, and chronic obstructive lung disease among others. These comorbid illnesses may have a considerable impact on the patient's tolerance to chemotherapy and hence influence the use of chemotherapy.

Our results suggest that the use of chemotherapy is increasing over time. For many years, 5-fluorouracil was the only active agent available in the management of patients with advanced CRC. More recently access to several novel agents including two cytotoxic agents, irinotecan and oxaliplatin, and three humanized monoclonal antibodies, including bevacizumab and cetuximab and panitumumab that target vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor, respectively, has resulted in significant improvement in survival of patients with stage IV CRC (3-6). With the availability of novel agents in the management of advanced CRC, we noted an approximately 25% increase in the use of chemotherapy. A Canadian study also demonstrated similar findings (18). Between 2003-04 (pre-bevacizumab era) and 2006 (bevacizumab era), the proportion of patients treated with systemic therapy for stage IV CRC significantly increased from 61.1% to 67.6%. In addition, the likelihood of the use of chemotherapy was higher in patients who underwent surgical resection of primary tumor or metastasectomy. Between 30% and 38% of patients diagnosed with stage IV CRC undergo one or more major surgical procedures (19). Surgical intervention may be performed with a curative intention or for symptomatic palliation (20). Selected patients with metastases limited to the lung and or liver can be cured with metastasectomy and adjuvant use of chemotherapy. The better prognosis of patients with limited disease burden supports a greater use of chemotherapy in such patients (3,20).

Our results revealed a sex ratio difference of 1.3:1. The incidence rates of CRC have been decreasing for most of the past two decades, which has largely been attributed to increases in the use of screening tests. Overall, incidence rates are lower in women than men, with a particularly striking discrepancy between premenopausal women and age-matched men (21,22). The estimated age standardized incidence of colorectal cancer in Canada, in 2014, is 59.4 per 100,000 cases in male versus 39.8 per 100,000 cases in female (23).

There are several limitations of this study. It is a retrospective study that was performed before the era of monoclonal antibodies. With the growing number of novel therapies in the management of colorectal cancer and the increasing awareness of the benefit of systemic therapy in advanced CRC, our results may not reflect the current clinical practice. Furthermore, in this study we did not assess the role of nonmedical factors such as ethnicity, socioeconomic status, family support and patients' perspectives on benefits and toxicities of treatment that can affect their likelihood of receiving chemotherapy. Data regarding variation in the use of chemotherapy, in relationship with various sociocultural variables in stage IV CRC, are scarce and are mostly limited to the use of adjuvant therapy. For instance, Potosky et al. investigated the disparity in the use of adjuvant therapies according to age, sex, and race/ethnicity and found differential uses of chemotherapy in elderly or African American patients with stage II & III CRC (24). Mcleod also showed that patients' characteristics, the areas in which they are resident, and the hospitals to which they are referred impact upon the type of treatment they receive (25). However, this analysis was not limited to stage IV CRC. We have undertaken a cohort study involving patients diagnosed during the period of 2006-2010 to validate our findings. In this study, information about various area level variables will be collected to assess their influence on the use of palliative chemotherapy. The research will also explore the relationship between the distance to the cancer center and the use of chemotherapy in patients with stage IV CRC.

In conclusion, this first large population-based study using various clinical variables including performance status demonstrates that the use of palliative chemotherapy is increasing. In addition to known variables such as good performance status and comborbid illness, patients who are treated with curative intent or who undergo resection of the primary tumor are more likely to receive chemotherapy. Despite the known benefit of chemotherapy in elderly patients with CRC, a differential use of cancer therapy is noted in this population. Future research to clarify patients' preference for chemotherapy is warranted, in order to minimize age-related bias on treatment decisions.

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Table 7.1: Baseline characteristics of patients who received chemotherapy and patients in the control group who did not receive chemotherapy.

Variables (Mean)	Total patients N=1237 (%)±SD	Chemotherapy N=580 (%)±SD	Control N=657 (%)±SD	P value
Median age years	70 (range: 22-98)	65 (22-89)	75 (33-98)	<0.001
Age >65 years	812 (65.6)	300 (51.7)	512 (77.9)	<0.001
Male	703 (56.8)	340 (58.6)	363 (55.3)	0.13
Comorbid illness	764 (61.8)	333 (57.4)	431 (65.6)	0.002
ECOG PS ≥2	294 (23.8)	64 (11)	230 (35)	<0.001
Active smoker	159 (12.9)	82 (14.1)	77 (11.7)	0.23
Rectal tumors*	386 (31.2)	184 (31.7)	202 (30.7)	0.37
Grade 3 cancer	234 (18.9)	109 (18.8)	125 (19)	0.48
Extra-hepatic disease	619 (50)	291 (50.2)	328 (49.9)	0.48
Metastases≥2 sites	360 (29.1)	167 (28.8)	193 (29.4)	0.43
Symptomatic disease	483 (39)	222 (38.3)	261 (39.7)	0.32
Albumin g/l	34.3±5.5	35.5±5.3	33.3±5.5	<0.001
Alkaline phosphatase U/l	187±234	179±191	200±266	0.20
Bilirubin um/l	13.2±24.8	11.7±24.6	14.7±24.9	0.04
BUN mm/l	5.8±4.4	5.1±2.6	6.5±5.5	<0.001
Creatinine um/l	88.1±30.8	83.7±28.4	92.0±32.4	<0.001
CEA mcg/l	253±1532	368±2155	152±550	0.013
Hemoglobin g/l	118±16	120±17	117±15	0.001
Sodium <135 mEq/l	168 (13.6)	72 (12.4)	96 (14.6)	0.14
White blood cell count ≥12 x 10^9/l	222 (17.9)	91 (15.7)	131 (19.9)	0.03
Received radiation	185 (15)	125 (21.6)	60 (9.1)	<0.001
Resection of primary tumor	881 (71.2)	469 (80.9)	412 (62.7)	<0.001
Metastasectomy	194 (15.7)	130 (22.4)	64 (9.7)	<0.001

*Rectum or recto-sigmoid disease, SD=standard deviation

Table 7.2: Univariate correlation between various clinicopathological variables and the use of chemotherapy in patients with stage IV colorectal cancer.

Variables	Odd Ratio	95% Confidence Interval	P value
Age ≤65 years	3.30	2.58-4.22	<0.001
Male	1.15	0.92-1.44	0.23
No comorbid illness	1.42	1.12-1.78	0.003
ECOG PS <2	4.34	3.20-5.89	<0.001
Extra-hepatic disease	1.01	0.81-1.26	0.93
Symptomatic disease	1.06	0.85-1.34	0.60
Albumin <35 g/l	4.53	3.54-5.78	<0.001
Alkaline phosphatase <100 IU	2.17	1.68-2.80	<0.001
Bilirubin <26 mm/l	2.15	1.20-3.83	<0.001
Sodium ≥136 meq/l	1.21	0.87-1.68	0.26
BUN <8 mm/l	2.35	1.55-3.57	<0.001
Creatinine <120 mm/l	1.24	0.81-1.91	0.32
Hemoglobin ≥120 g/l	1.91	1.52-2.40	<0.001
White blood cell count <12 x 10^9/l	1.34	1.0-1.80	0.052
Metastases <2 sites	1.01	0.76-1.24	0.82
Surgical resection of primary tumor	2.51	1.94-3.26	<0.001
Received radiation	2.73	1.96-3.81	<0.001
Metastasectomy	2.68	1.94-3.70	<0.001
Time Period*	1.44	1.15-1.81	0.001

* Diagnosed ≥ Jan 1st 2000 during the era of second line therapy.

Table 7.3: Multivariate correlation between various clinicopathological variables and the use of chemotherapy in patients with stage IV colorectal cancer.

Variables	Odd Ratio	95% Confidence Interval	P value
Age ≤65 years	3.82	2.59-5.61	<0.001
Male	1.19	0.90-1.56	0.22
No comorbid illness	2.87	1.34-6.16	0.007
ECOG PS <2	2.72	1.94-3.82	<0.001
Albumin ≥35 g/l	3.26	2.44-4.36	<0.001
BUN <8 mm/l	2.24	1.40-3.59	0.001
Hemoglobin ≥120 g/l	1.48	0.93-2.34	0.10
Surgical resection of primary tumor	2.00	1.47-2.73	<0.001
Received radiation	2.03	1.38-3.00	<0.001
Metastasectomy	3.60	1.82-7.10	<0.001
Time Period*	1.85	1.41-2.42	<0.001
Age X hemoglobin	0.45	0.27-0.82	0.007
comorbid illness x metastesectomy	0.29	0.13-0.66	0.003

* Diagnosed ≥ Jan 1st 2000 during the era of second line therapy.

Figure 7.1: Prevalence of chemotherapy in patients with advanced colorectal cancer in two different time periods in relationship with the availability of novel therapy.

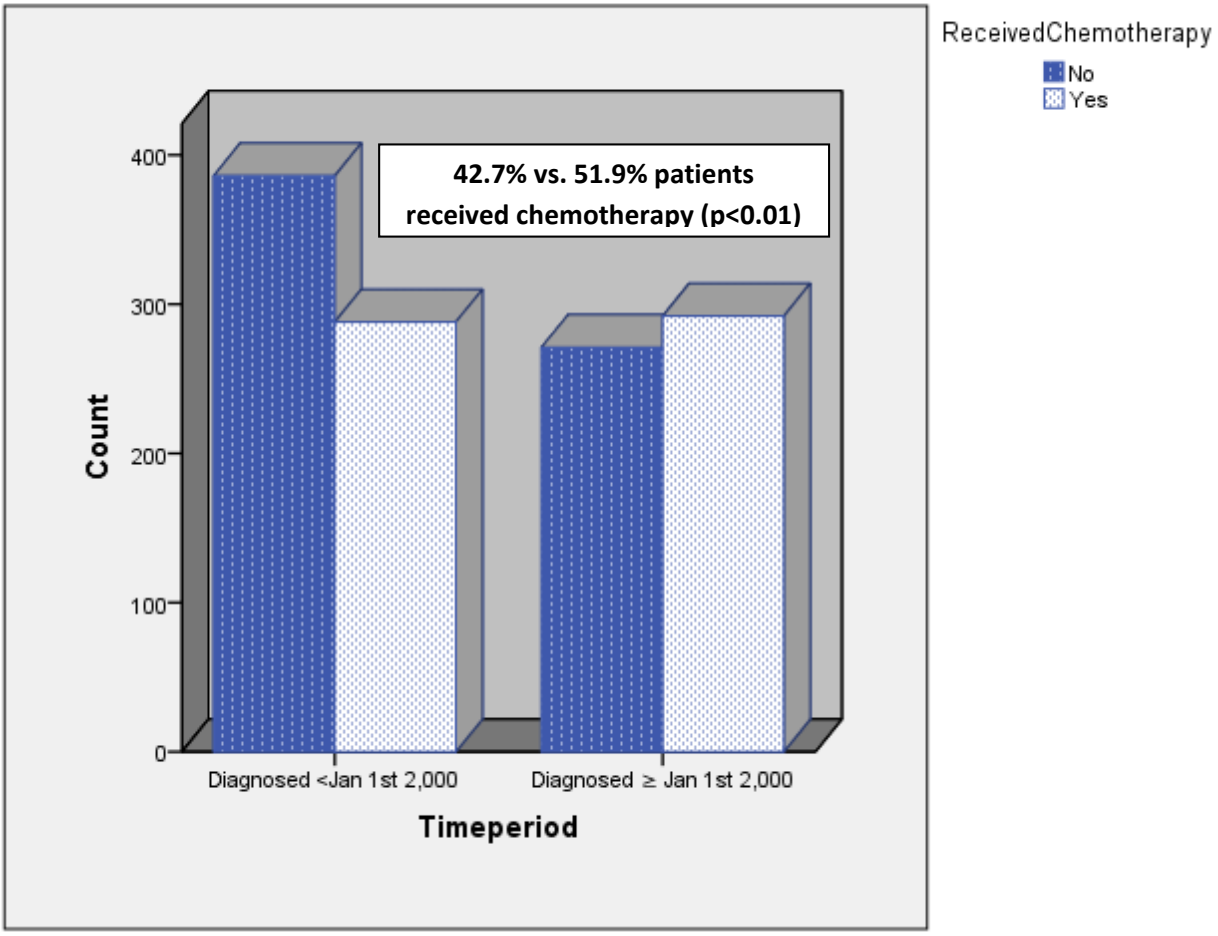
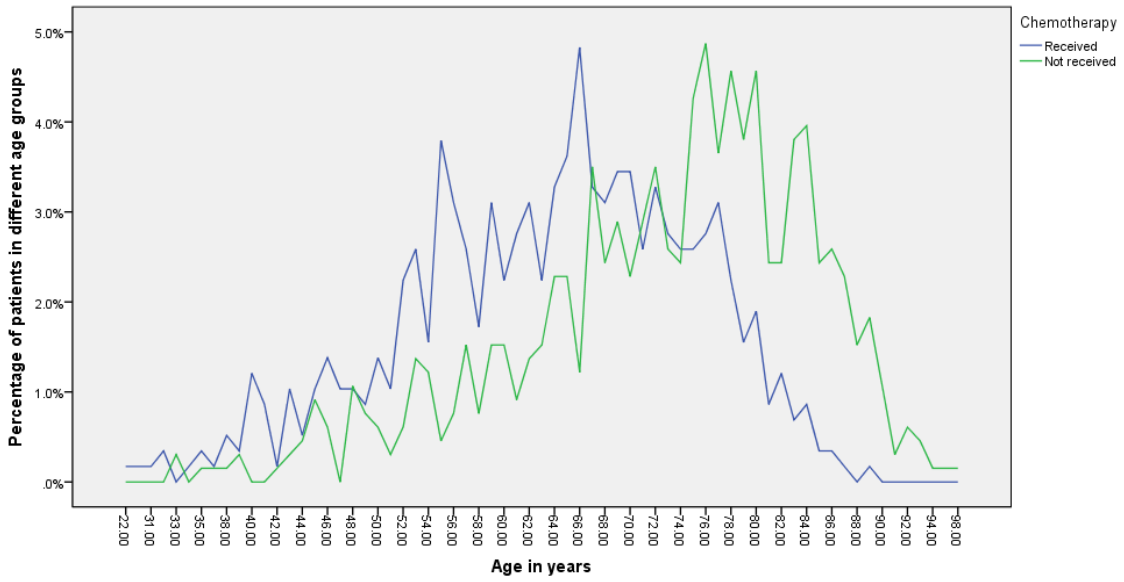


Figure 7.2: Association between increasing age (2A) and year of diagnosis (2B), and the use of chemotherapy in patients with advanced colorectal cancer.

7.2A



7.2B

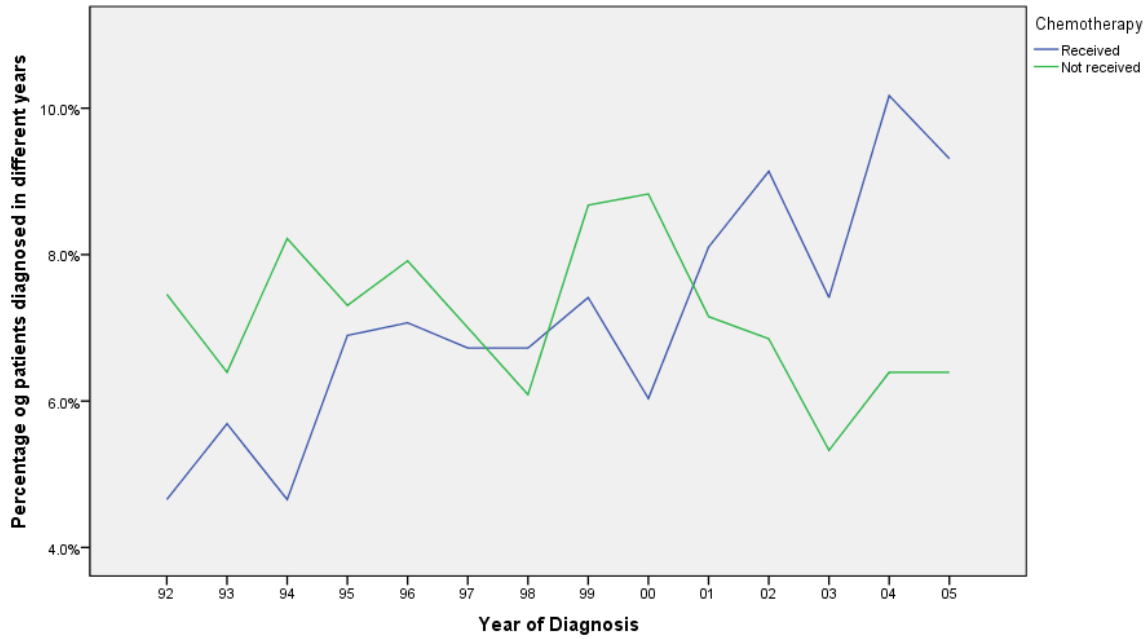
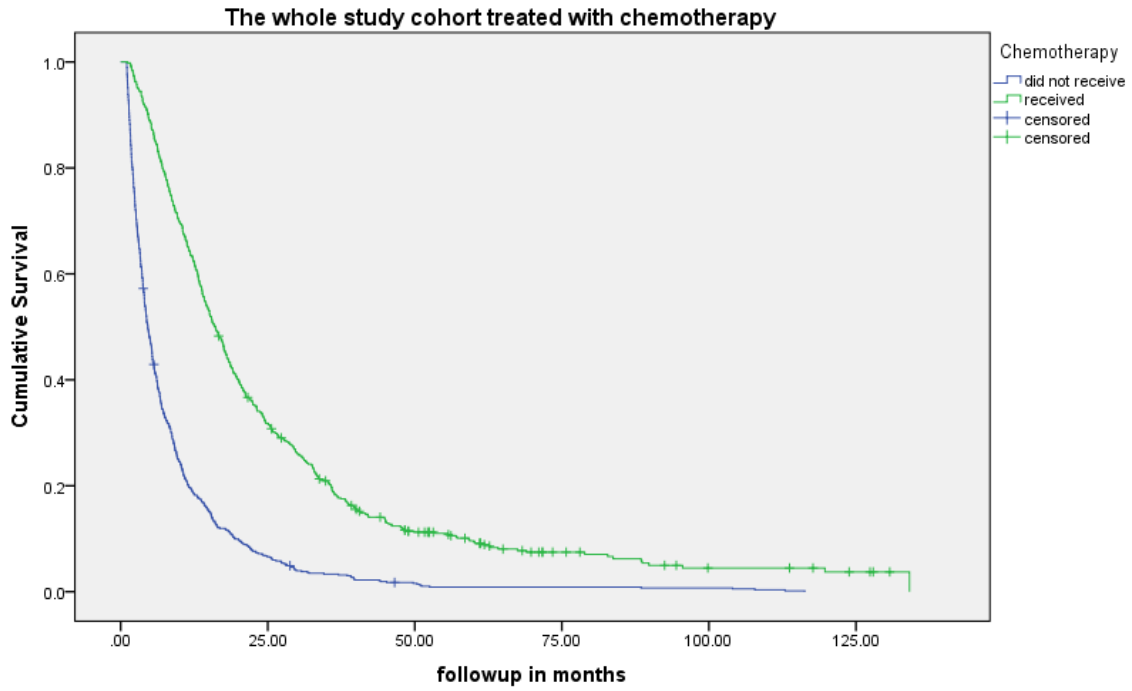
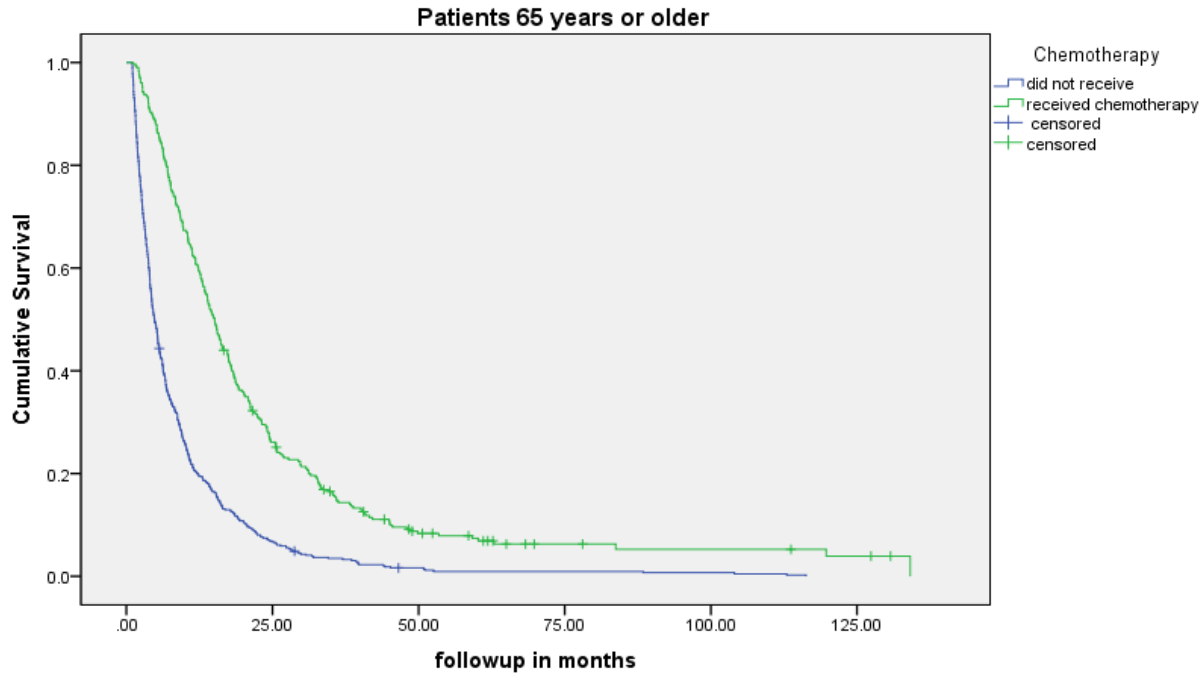


Figure 7.3: Survival of the whole cohort (3A) and subcohort of patients ≥65 year old (3B) with advanced CRC who received chemotherapy versus best supportive care.

7.3A



7.3B



CHAPTER 8 – CAMPANION STUDY II: THE IMPORTANCE OF REGIONAL LYMPH NODES STATUS IN METASTATIC COLORECTAL CANCER

The pathological staging such as the degree of tumor infiltration through the bowel wall, histological grade, number of examined lymph nodes, and nodal metastases are known prognostic factors in the early-stage CRC. However, their significance in patients with stage IV CRC remains unknown. The present chapter addresses the importance of regional lymph nodes status in patients with metastatic CRC.

Our research findings suggest that primary tumor resection in patients with stage IV CRC improves survival independent of chemotherapy, metastasectomy, comorbid illness, and performance status. Given the fact that there is a very little knowledge about the prognostic significance of primary tumor-related factors including regional nodes status in stage IV CRC, in this companion study we explored the relationship between nodal status or the ratio of metastatic to examined lymph node (LNR) and survival in patients with metastatic CRC. The study findings were presented at the European Society of Medical Oncology (ESMO) 2015 Annual Meeting in Vienna, Austria and at the Gastrointestinal Cancers Symposium 2016 Annual Meeting in San Francisco, USA in the poster sessions. The results were published in the Annals of Surgical Oncology "*Ahmed S, Leis A, Chandra-Kanthan S, Fields A, Zaidi A, Abbas T, Le D, Reeder B, Pahwa P.Regional Lymph Nodes Status and Ratio of Metastatic to Examined Lymph Nodes Correlate with Survival in Stage IV Colorectal Cancer. Ann Surg Oncol. 2016 Mar 25. [Epub ahead of print]*".

8.1 Abstract

Background: Although lymph nodes status and the ratio of metastatic to examined lymph node (LNR) are important prognostic factor in early-stage colorectal cancer (CRC), their significance in patients with metastatic disease remains unknown. The study aims to determine prognostic importance of nodal status and LNR in patients with stage IV CRC.

Methods: A cohort of 1109 eligible patients who were diagnosed with synchronous metastatic CRC in Saskatchewan during 1992-2010 and underwent primary tumor resection was evaluated. We conducted the Cox Proportional multivariate analyses to determine the prognostic significance of nodal status & LNR.

Results: Median age was 70 years (22-98) and M:F was 1.2:1. Rectal cancer was found in 26% patients; 96% had T3/T4 tumor, and 82% had node positive disease. The median LNR was 0.36 (0-1.0). Fifty-four percent patients received chemotherapy. Median overall survival of patients who had LNR of < 0.36 and received chemotherapy was 29.7 months (95% CI: 26.6-32.9) compared with 15.6 months (95%

CI: 13.6-17.6) with LNR of ≥ 0.36 ($p < 0.001$). On multivariate analyses, no chemotherapy, HR: 2.36 (95% CI: 2.0-2.79); not having metastasectomy, HR: 1.94 (95% CI: 1.63-2.32); LNR ≥0.36, HR: 1.59 (95% CI: 1.38-1.84); nodal status, HR 1.34 (95% CI: 1.14-1.59); and T status, HR 1.23 (95% CI: 1.07-1.40) were correlated with survival. Test for interaction was positive for LNR and high-grade cancer, HR1.51 (95% CI: 1.10-2.10).

Conclusions: Our results suggest that nodal status and LNR are important prognostic factors independent of chemotherapy and metastasectomy in stage IV CRC patients.

8.2 Introduction

Although pathological staging such as the degree of tumor infiltration through the bowel wall, histological grade, number of examined lymph nodes, and nodal metastases are important prognostic factors in the early-stage CRC, their significance in patients with stage IV CRC remains unknown. Lymph node involvement is one of the most important prognostic variables in early-stage CRC (1). Adjuvant chemotherapy is recommended for node-positive CRC. In addition to nodal involvement, the numbers of lymph nodes harvested and examined are important prognostic factors. A systematic review examined relationship of the number of lymph nodes retrieved following colon resection and survival. Of 17 studies involving a total of 61,371 patients, 16 showed a positive association between the number of lymph nodes examined and survival in stage II and III colon cancer patients (2). Nevertheless, a higher number of nodes examined do not necessarily predict having more nodes involved. There is evidence that the ratio of metastatic to examined lymph nodes (LNR) is an important prognostic factor in early-stage CRC (3).

Approximately 20% patients are diagnosed with synchronous metastatic CRC with an in situ primary tumor. Combination chemotherapy with a biological agent is the standard treatment for most patients with newly diagnosed stage IV CRC (1). The optimal management of primary tumor in these patients remains controversial. We have reported that surgical resection of primary tumor improves survival independent of chemotherapy, metastasectomy, and performance status in patients with stage IV CRC (4,5). We hypothesized that regional nodal status in stage IV CRC has prognostic importance and correlates with survival. In this retrospective cohort study, we examined the relationship between nodal status or LNR and survival in patients with stage IV CRC.

8.3 Methods

8.3.1 Study Population

The University of Saskatchewan's Research Ethics Board approved the study protocol. The study population was comprised a cohort of adult patients with newly diagnosed stage IV adenocarcinoma of colon and rectum who underwent resection of primary tumor, from January 1992 to December 2010, in the province of Saskatchewan, Canada. Patients with other histological diagnoses or with an intact primary tumor were excluded. The Saskatchewan Cancer Registry prospectively collects and updates its Registry. Using the Saskatchewan Cancer Registry, eligible patients were identified. A trained research associate reviewed the individual patient records and abstracted data. All patients were followed until their death or until June 2014 when the data entry was closed.

8.3.2 Statistical Analysis

Overall survival was defined as "time from the diagnosis of stage IV CRC to death from any cause". The Kaplan-Meier method was used to estimate survival. The log-rank tests were performed to compare survival distribution of different groups. Multivariate analyses were performed to determine the prognostic significance of nodal status and the LNR. The continuous variables were dichotomized by specifying various cutoff points such as abnormal laboratory values. For LNR, we used median value to divide the cohort into two groups. The Cox proportional hazard model was used, and the hazard ratio and its 95% CI were estimated. The following variables were examined with respect to their prognostic significance: age (<70 vs. ≥70), gender, major comorbid illness as per Charlson comorbid index, ECOG performance status (<2 vs. ≥2), active smoking, previous history of cancer, serum creatinine (≥120 vs. <120 mm/l), BUN (≥8 vs. <8 mm/l), albumin (≥36 vs. <36 g/l), bilirubin (≥26 vs. <26 um/l), alkaline phosphatase (≥120 vs. <120 mm/l), hemoglobin (≥120 vs. <120 g/l), WBC (≥11 vs. <11 x 10^9/l), platelet (≥450 vs. <450 x10^9/l), CEA (≥5 vs. <5 mcg/l), site (colon vs. rectal), grade (3 vs. <3), symptomatic disease, extra-hepatic metastases, stage (stage IVa vs. IVb), mucinous tumor, T status, LNR (<0.36 vs. ≥0.36), number of lymph nodes removes (≥12 vs. r <12), nodal status, use of any chemotherapy, second-generation chemotherapy, metastasectomy, and radiation therapy. We used log-log survival curves to assess the proportional hazards assumption for the variables examined in the final mathematical model.

All variables with P<0.05, on univariate analysis, were examined, in a multivariate model to assess their correlation with survival. The likelihood ratio test and *t* test were used for each variable to determine if the addition of independent variable of interest adds significantly to the prediction of survival in the model. Test for interaction was performed for LNR and the variables that were significantly correlated with survival in the univariate analysis. A two-sided P-value of <0.05 were considered to be statistically significant. Because the time period for the study was long, a secondary analysis was performed in a sub-cohort of patients diagnosed from January 2006 to December 2010 during the period of combination chemotherapy and biologics. The SPSS version 23.0 was used for statistical analysis (SPSS Inc. Chicago, IL).

8.4 Results

8.4.1 Patients Characteristics

A total of 1257 patients with stage IV CRC who underwent resection of primary tumor during the study period were identified. Of these, 148 patients did not have information about lymph nodes status and were excluded (**Figure 8.1**). Median age of eligible patients was 70 years (range: 22-98 years) and M:F was 1.2:1. Two hundred and eighty-three (25.5%) patients had rectal or rectosigmoid cancer; 1161 (95.7%) had T3/T4 tumor (mostly T4a), and 353 (31.8%) had stage IVb disease (**Table 8.1**). A total of 905 (81.6%) patients had node-positive disease. Of these, 407 (45.0%) had N1 (up to 3 node were involved) and 498 (55.0%) had N2 (4 or more nodes involvement) disease. The median LNR was 0.36 (0-1.0). Based on median LNR score of 0.36 the patients' cohort was divided into two groups. Group I with LNR of <0.36 and group II with LNR of ≥0.36. The median number of lymph nodes removed was 10 (range: 1-55); 10 (1-46) in group

with LNR ≥36 compared with 12 (1-55) in the group with LNR<36 (p=0.003). The median number of positive lymph node was 3 (0-46): 6 (1-46) in the group with LNR ≥0.36 compared with 1 (0-10) in the group with LNR<0.36 (p<0.001). A total of 597 patients (53.8%) received chemotherapy; of those 44% received second-generation chemotherapy (FOLFIRI and or FOLFOX with a biologic). Also, 537 patients (47.8%) had extrahepatic disease, 286 (51.7%) in the group with LNR of ≥0.36 compared with 244 (43.9%) patients with LNR <0.36 (p=0.01). Lungs, peritoneum and distant lymph nodes were the most common extrahepatic sites. In addition, patients with LNR ≥0.36 has significantly increased proportion of high-grade tumor or mucinous cancer.

8.4.2 Survival

Median follow-up period was 13 months (inter-quartile range: 4.6-27.0 months). Median overall survival (OS) of whole cohort was 13 months (95% CI: 11.90-14.24). The group with LNR of <0.36 had median OS of 18 months (95% CI: 16.14-19.86) compared with 8.9 months (95% CI: 7.60-10.25) with LNR of ≥0.36 (p<0.001) [**Figure 8.2**]. A subcohort of 597 patients who received chemotherapy had median OS of 21 months (95% CI:18.79-23.21). Among 597 patients who received chemotherapy the group with LNR of <0.36 had median OS of 29.73 months (95% CI: 26.60-32.87) compared with survival of 15 months (95% CI: 13.62-17.65) if they had LNR of ≥0.36 (P<0.001) [**Figure 8.3**].

With respect to lymph node status, the median OS of patients with node-negative disease who received chemotherapy was 31.4 months (95% CI: 25.66-37.20) compared with 19.4 months (95% CI: 17.96-20.84) if they had node-positive disease (p=0.002). Among patients with node-positive disease, patients with up to 6 node positive disease had median OS of 21months (95% CI:18.3-23.7) compared with 16 months (95% CI:13.1-18.9) if they had more than 6 nodes involved by the cancer (<0.001) [**Table 8.2] [Figure 8.4]**.

In a subgroup of 237 patients who underwent metastasectomy, patients with node-negative disease had median OS of 53.5 months (95% CI: 38.1-68.9) compared with 39.8 (95% CI: 31.1-48.4) if they had regional lymph nodes involvement (p=0.003).

8.4.3 Multivariate Modelling

On univariate analysis several patients-related factors (age, performance status, and Chalrson comorbid index); tumor-related factors (T status, grade 3 tumor, colon cancer, mucinous disease, stage IVb cancer, LNR, node positive disease, number of node harvested, and symptomatic primary tumor); interventions (use of any chemotherapy, second-generation chemotherapy, metastasectomy, and radiation therapy) and abnormal laboratory values (low albumin, elevated alkaline phosphatise, elevated BUN, abnormal CEA, elevated bilirubin, anemia, and leukocytosis) were correlated with survival (**Table 8.3**). Test for interaction was significant for LNR and serum creatinine, tumor grade, second-generation chemotherapy, and radiation therapy. In a multivariate model after adjustment for other variables, LNR ≥0.36 correlated with survival with hazard ratio for mortality of 1.59 (95% CI: 1.38-1.84). In addition, chemotherapy, metastasectomy, second-generation chemotherapy, T status, stage IVb disease, elevated bilirubin, alkaline phosphatase,

CEA, leukocytosis, and tumor location were correlated with survival (**Table 8.4**). In the final model, only the interaction between LNR and tumor grade was significant. The median OS of patients with low- or intermediate-grade tumor was 23.7 months (95% CI: 21.20-26.20) compared with 15 months (95% CI: 12.80-17.21) in patients who had high-grade tumor (p=0.002). Patients with low-grade tumor and LNR < 0.36 had median OS of 30 months (95% CI: 27.10-32.92) compared with 11.8 months in patients with high-grade tumor with LNR ≥0.36 (P<0.001).

Due to presence of multicollinearity between LNR and lymph nodes status, a separate model (model B) was fitted. In this model lymph node status (positive vs. negative) was used instead of LNR. Lymph node status was correlated with survival with HR for mortality of 1.34 (95% CI: 1.14-1.59) for node-positive disease. In a subcohort of patients who underwent metastasectomy, both LNR using a cut-off of 0.36 and nodal status, independent of chemotherapy and other prognostic variables, were correlated with survival, HR of 2.38 (95%: 1.64-3.47) for LNR ≥ 36 and 1.57 (95% CI: 1.05-2.34) for node-positive disease.

8.4.4 Secondary Analysis

In a subcohort of 308 eligible patients who were diagnosed with synchronous metastatic CRC and underwent primary tumor resection during the period of modern chemotherapy both LNR and nodal status correlated with survival. Median overall survival of patients with low LNR who received chemotherapy was 45 months (34.9-55.1) compared with 20 months (16.3-23.7), if they had high LNR (p < 0.001). On multivariate analyses, no chemotherapy, HR: 2.53 (1.77-3.61), not having metastasectomy, HR: 2.30 (1.63-3.24), no biologics, HR: 1.80 (1.27-2.56), nodal status, HR 1.87 (1.25-2.80), and LNR, HR: 1.64 (1.26-2.13) were correlated with survival.

8.5 Discussion

Our results suggest that lymph node status and LNR are important prognostic factors and correlate with survival independent of systemic therapy and other patient- and tumor-related factors in patients with stage IV CRC.

Colorectal cancer spread by both lymphatic and hematogenous dissemination. Furthermore, contiguous and transperitoneal routes are important ways of dissemination of the disease. The most common metastatic sites are the regional lymph nodes, liver, lungs, and peritoneum (1,6). In early-stage CRC, both the number of examined lymph node and presence of nodal metastases guide the use of adjuvant therapy. The LNR has been proposed as a better prognostic factor than the number of metastatic lymph nodes (7-9). If the total nodes examined remains unchanged but the number of positive nodes increases, the LNR will increase.

Our results support that regional nodal status is not only important in early-stage CRC but also in stage IV CRC. Since LNR and lymph node status are linearly dependent covariate, they were fitted in separate models to assess their prognostic significance. The present study revealed an inverse relationship between number of positive regional lymph nodes or LNR and survival. For example, patients with node-negative disease had median OS of 31 months compared with 16 months if they had 7 or more regional node were involved. The effect size was larger in patients who were treated with second-generation chemotherapy (FOLFIRI and or FOLFOX with a biologic) or during the period of combination chemotherapy and biologics. Both LNR and lymph node status can be used

as comparable prognostic markers in patients with stage IV CRC undergoing resection of the primary tumor. Notably, nodal status and LNR were important prognostic variables in patients who underwent metastasectomy and independently correlated with survival.

The histologic grade of a tumor provides prognostic information. Poorly differentiated tumors are known to pursue a more aggressive course than their well-differentiated counterparts do (12). We noted a positive interaction between tumor grade and LNR. High-grade tumors had a higher number of metastatic nodes and higher LNR. For example, 45.7% low-grade tumors had LNR ≥0.36 compared with 64.6% high-grade tumors had LNR ≥0.36. Patients with LNR ≥0.36 and low-grade tumor had a better median OS of 15.9 months compared with 11.8 months if they had high-grade tumor.

Only few studies have evaluated the prognostic significance of regional lymph nodes in stage IV CRC. Our findings support a previous study by Thomay et al. which examined the prognostic effect of regional nodal metastases in stage IV CRC. In their study, an increasing number of positive regional nodes and LNR correlated with inferior survival (13). Derwinger and Gustavsson also evaluated importance of regional nodal status in patients with stage IV CRC and found that the lymph node ratio along with chemotherapy and tumor grade correlated with overall survival (14). In contrast to studies by Derwinger and Gustavsson and Thomay et al. which were performed in patients treated at selected centers, our study was a population-based study with limited selection bias. Furthermore, unlike Thomay et al., who included patients with previous diagnosis of early stage CRC and metachronous metastases, our study population was comprised only patients with synchronous metastatic CRC. Similar to Thomay et al. the present study included patients who were treated with both older and modern chemotherapy regimens. Because the study spanned a long period, we examined the study period as a prognostic variable. When the year of diagnosis was evaluated as a continuous variable, it was correlated with survival (not shown). We performed a secondary analysis involving the patients diagnosed during the period of combination chemotherapy and biologics and noted prognostic significance of regional lymph nodes during the period of modern chemotherapy.

The mechanisms underlying the relationship between the regional node status and survival in stage IV CRC remain uncertain. It is plausible that lymph node status signifies underlying tumor biology. Unlike early-stage CRC where LNR and nodal status reflect accurate tumor staging, efficacious surgical intervention, and superior quality of pathology service and correlate with better survival, other factors may account for difference in survival in stage IV CRC. For example, a greater host immune response among patients with a larger negative lymph node count, or other unknown underlying molecular/biological characteristics of tumor may account for difference in survival.

Of note, the depth of local tumor invasion (T status) was found to be an independent prognostic variable. Majority of patients with stage IV CRC had T3 or T4 (mostly T4a tumor). When T status was examined as a continuous variable, it was independently correlated with survival. The depth of local tumor invasion is a well-known prognostic factor in node-positive early-stage colorectal cancer (15). However, relative to regional lymph node status the association between T status and lymph node was weak.

One of the limitations of the current study is that we do not have information about BRAF mutation, which is reported in about 5-11% stage IV CRC and is an important prognostic marker (16). It is not known if differential distributions of BRAF mutation in the study groups have accounted for difference in survival in relation to the regional nodal status. Recently, Gleisner et al. using a complex statistical model examined the interactive effect of total number of lymph nodes examined (TNLE) and the number of metastatic lymph nodes (NMLN) on survival in patients with early-stage CRC (17). The author concluded that the combined effect of NMLN and TNLE is complex and may not appropriately represented by the LNR and proposed N score as an alternative prognostic biomarker. Nevertheless, other investigators have not validated the N score.

In summary, our results suggest that the regional lymph node status including the number of negative lymph nodes or the ratio of metastatic to examined lymph node are important prognostic factors and correlate with survival in patients with stage IV CRC. Furthermore, regional nodal status correlates with survival in patients treated with curative resection. To our knowledge, this is the only population-based study that has addressed this question by reviewing individual patient's data. Future studies are required to confirm our findings and to elucidate the mechanism by which nodal status and LNR affect survival of patients with stage IV CRC.

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Table 8.1: Characteristics of patients in the entire cohort and subgroups of patients with the ratio of metastatic to examined lymph node (LNR) of 0.36.

Variables	Study cohort N=1109	Group 1 N=553 LNR ≥0.36	Group 2 N=556 LNR <0.36	P value
Demographic				
Median age	70 (22-98)	70 (22-92)	69 (31-98)	0.72
Age 70 years or greater	555 (50)	278 (50.3)	277 (49.7)	0.90
Secondary Cancer	164 (14.8)	74 (13.4)	90 (16.2)	0.20
ECOG performance status 2 or more	249 (22.5)	137 (24.8)	112 (20.1)	0.07
Charlson comorbidity index	279 (25.2)	137 (24.8)	142 (25.5)	0.78
Mean Charlson score	9.6±1.50	9.6±1.47	9.6±1.49	0.76
Male	618 (55.7)	312 (56.4)	306 (55)	0.67
Active smoker	197 (17.8)	86 (15.6)	111 (20)	0.06
Mean laboratory values				
Albumin g/l	34.2±6	34.1±6	34.5±6	0.32
Alkaline phosphatase U/l	174±248	198±292	150±191	0.001
Bilirubin ug/l	11.9±17.7	12.8±21.1	11.0±13.6	0.093
Blood urea nitrogen mm/l	5.6±4.1	5.7±4.2	5.5±3.9	0.40
CEA ug/l	258±1328	297±1446	220±1200	0.33
Creatinine um/l	88.1±32.6	88.1±32.1	88.0±33.0	0.94
Hemoglobin g/l	119±15.8	118±15.3	120±16	0.03
Platelet 10^9/l	343±119	353±117	334±120	0.009
White blood cell count 10^9/l	8.8±4.8	8.9±3.2	8.7±5.9	0.46
Treatment				
Chemotherapy	597 (53.8)	282 (51.0)	315 (56.7)	0.06
Second or third line therapy	272 (45.6)	128 (45.3)	144 (45.7)	0.29
FOLFIRI or FOLFOX± biologics	266 (44.5)	123 (43.6)	143 (45.4)	0.18
Radiation therapy	144 (13)	69 (12.5)	75 (13.5)	0.65
Metastasectomy	237 (21.4)	98 (17.7)	139 (25)	0.03
Metastatic sites				
Liver	830 (74.8)	420 (75.9)	410 (73.7)	0.40
Extra-hepatic disease	530 (47.8)	286 (51.7)	244 (43.9)	0.01
Stage IVb	353 (31.8)	208 (37.6)	145 (26.1)	<0.001
Primary Tumor				
T3 or 4 tumor	1061 (95.7)	533 (96.4)	528 (95)	0.32
Node Positive disease	905 (81.6)	553 (100)	352 (63.3)	<0.001
0	204 (18.4)	0	204 (36.7)	<0.001
1-6 positive nodes	640 (57.7)	294 (53.2)	346 (62.2)	<0.001
More than 6 positive nodes	265 (23.9)	259 (46.8)	6 (1.1)	<0.001
Median number of nodes removed	10 (1-55)	10 (1-46)	12 (1-55)	0.023
Median number of nodes involved	3 (0-46)	6 (1-46)	1 (0-10)	<0.001
Grade 3	246 (22.2)	159 (28.7)	87 (15.6)	<0.001
Mucinous	178 (16.1)	104 (18.8)	74 (13.3)	0.014
Rectum or rectosigmoid tumor	283 (25.5)	135 (24.4)	148 (26.6)	0.22
Symptomatic primary tumor	523 (47.2)	273 (49.4)	250 (45.2)	0.14

Biologics= cetuximab, panitumumab or bevacizumab; CEA= carcinoembryonic antigen; ECOG= Eastern Cooporative Oncology Group; FOLFIRI=Infusional 5-FU, leucovorin and irinotecan; FOLFOX=Infusional 5-FU, leucovorin and oxaliplatin;

Table 8. 2: Survival of patients in relationship with regional lymph node status.

Nodal Status	Median Overall Survival	95% Confidence Interval
All patients	21.0 months	18.79-23.21
Patients with more than 6 nodes involved	16.0 months	13.07-18.93
Patients with up to 6 nodes involved	21.0 months	18.34-23.66
Patients with node negative disease	31.4 months	25.66-37.20

Table 8. 3: Relationship between various clinicopathological variables and survival in univariate analysis.

Variables	HR (95% CI)	P value	HR (95% CI) for Interaction with node ratio	P value
Age ≥70 years	1.73 (1.53-1.96)	<0.001	0.89 (0.70-1.14)	0.35
Albumin <35 g/l	1.91 (1.69-2.17)	<0.001	1.09 (0.85-1.41)	0.49
Alkaline phosphatase >120 U/l	2.10 (1.81-2.33)	<0.001	1.06 (0.83-1.37)	0.64
Bilirubin ≥26 um/l	2.23 (1.65-3.0)	<0.001	0.88 (0.47-1.64)	0.69
BUN ≥8 mm/l	1.40 (1.14-1.73)	0.002	0.68 (0.45-1.05)	0.08
CEA ≥5 ug/l	2.24 (1.90-2.64)	<0.001	0.90 (0.65-1.25)	0.52
Charlson Comorbid Score	1.67(1.47-1.89)	<0.001	1.13 (0.88-1.45)	0.34
No chemotherapy (Any)	3.29 (2.89-3.740	<0.001	0.97 (0.76-1.25)	0.83
Colon tumor	1.43 (1.24-1.66)	<0.001	0.79 (0.59-1.06)	0.11
Creatinine ≥120 um/l	1.48 (1.18-1.86)	0.001	0.56 (0.35-0.89)	0.013
Current Smoking	0.92 (0.78-1.09)	0.33	0.92 (0.66-1.28)	0.63
ECOG performance status ≥2	2.53 (2.16-2.93)	<0.001	0.80 (0.60-1.07)	0.13
Extra-hepatic disease	1.10 (0.97-1.24)	0.16	1.09 (0.85-1.40)	0.49
Grade 3	1.45 (1.25-1.68)	<0.001	0.72 (0.53-0.99)	0.04
Hemoglobin <120 g/l	1.43 (1.26-1.62)	<0.001	1.24 (0.96-1.59)	0.08
Higher positive node ratio (LNR) ≥0.36	1.80 (1.59-2.04)	<0.001		
Less than 12 nodes removed	1.35 (1.19-1.55)	<0.001	0.99 (0.76-1.29)	0.95
Male gender	0.73 (0.86-1.11)	0.98	0.95 (0.74-1.22)	0.67
Not having metastasectomy	2.72 (2.30-3.21)	<0.001	0.74 (0.54-1.03)	0.078
Mucinous pathology	1.21 (1.03-1.43)	0.023	0.99 (0.71-1.39)	0.98
Nodal positive*	1.32 (1.12-1.55)	0.001		
Platelet count, ≥450 x10^9/l	1.06 (0.89-1.26)	0.54	1.29 (0.91-1.83)	0.15
Radiation	1.76 (1.46-2.13)	<0.001	1.52 (1.04-2.21)	0.029
Lack of second line Treatment	2.06 (1.78-2.38)	<0.001	1.55 (1.16-2.10)	0.003
Lack of second generation therapy**	2.10 (1.81-2.44)	<0.001	1.64 (1.22-2.20)	0.001
Secondary cancers	1.01 (0.85-1.20)	0.91	1.03 (0.73-1.45)	0.87
Stage IVb disease	1.45 (1.27-1.65)	<0.001	0.87 (0.67-1.145)	0.33
Symptomatic primary tumor	1.30 (1.15-1.47)	<0.001	0.94 (0.74-1.20)	0.62
T status	1.20 (1.06-1.36)	0.003	0.85 (0.67-1.09)	0.21
WBC count ≥11 x 10^9/l	1.73 (1.46-2.04)	<0.001	1.12 (0.79-1.58)	0.51

*Linearly dependent covariate **FOLFIRI (infusional 5-FU, leucovorin and irinotecan) and or FOLFOX (infusional 5-FU, leucovorin and oxaliplatin) with or without Biologics (cetuximab, panitumumab or bevacizumab); CEA= carcinoembryonic antigen; ECOG PS= Eastern Cooporative Oncology Group performance status; WBC=white blood cell;

Table 8.4: Multivariate analysis with variables independently correlated with superior survival in patients with stage IV colorectal cancer.

Variables	HR (95% CI)	P value	HR (95% CI)	P value
	Model A		Model B	
Age ≥70	1.21 (0.90-1.61)	0.20	1.16 (0.87-1.54)	0.32
Alkaline Phosphatase >120 U/l	1.33 (1.20-1.52)	<0.001	1.33 (1.16-1.52)	<0.001
Bilirubin ≥26 um/l	1.55 (1.13-2.11)	0.006	1.65 (1.21-2.25)	0.001
CEA ≥5 ug/l	1.67 (1.40-2.0)	<0.001	1.64 (1.38-1.96)	<0.001
Charlson Comorbid Score	1.30 (0.95-1.70)	0.10	1.20 (0.89-1.60)	0.22
No chemotherapy	2.36 (2.0-2.79)	<0.001	2.44 (2.07-2.89)	<0.001
Colon cancer	1.21 (1.05-1.41)	0.01	1.15 (0.99-1.38)	0.06
ECOG performance status ≥2	1.43 (1.22-1.68)	<0.001	1.39 (1.18-1.62)	<0.001
Grade III	1.10 (0.83-1.39)	0.56	1.43 (1.23-1.66)	<0.001
Higher positive node ratio ≥0.36	1.59 (1.38-1.84)	<0.001		
Not having metastasectomy	1.94 (1.63-2.32)	<0.001	1.96 (1.64-2.33)	<0.001
Node positive disease			1.34 (1.14-1.59)	0.001
Lack of second generation chemotherapy	1.46 (1.22-1.75)	<0.001	1.41 (1.17-1.69)	<0.001
Stage IVB disease	1.22 (1.10-1.40)	0.004	1.29 (1.12-1.47)	<0.001
T status	1.23 (1.07-1.40)	0.003	1.22 (1.07-1.40)	0.004
WBC ≥11 x 10^9/l	1.46 (1.22-1.74)	<0.001	1.53 (1.28-1.83)	<0.001
Grade* Higher positive node ratio ≥0.36	1.51 (1.10-2.10)	0.01		

Figure 8.1: Flow of information about eligible patients' cohort.

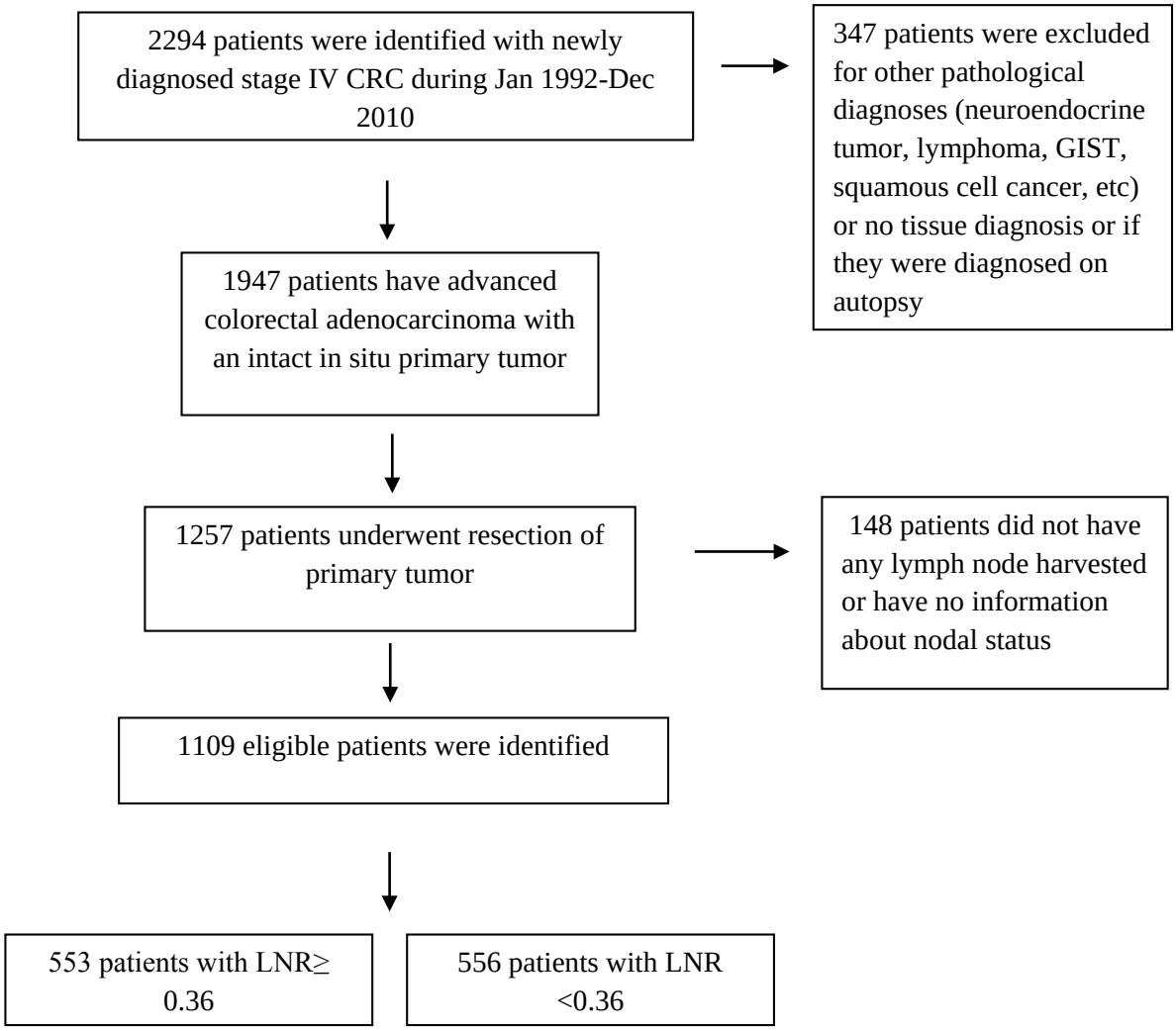


Figure 8.2: Survival of patients with stage IV colorectal cancer based on the ratio of metastatic to examined lymph node (LNR) using a median cutoff value of 0.36.

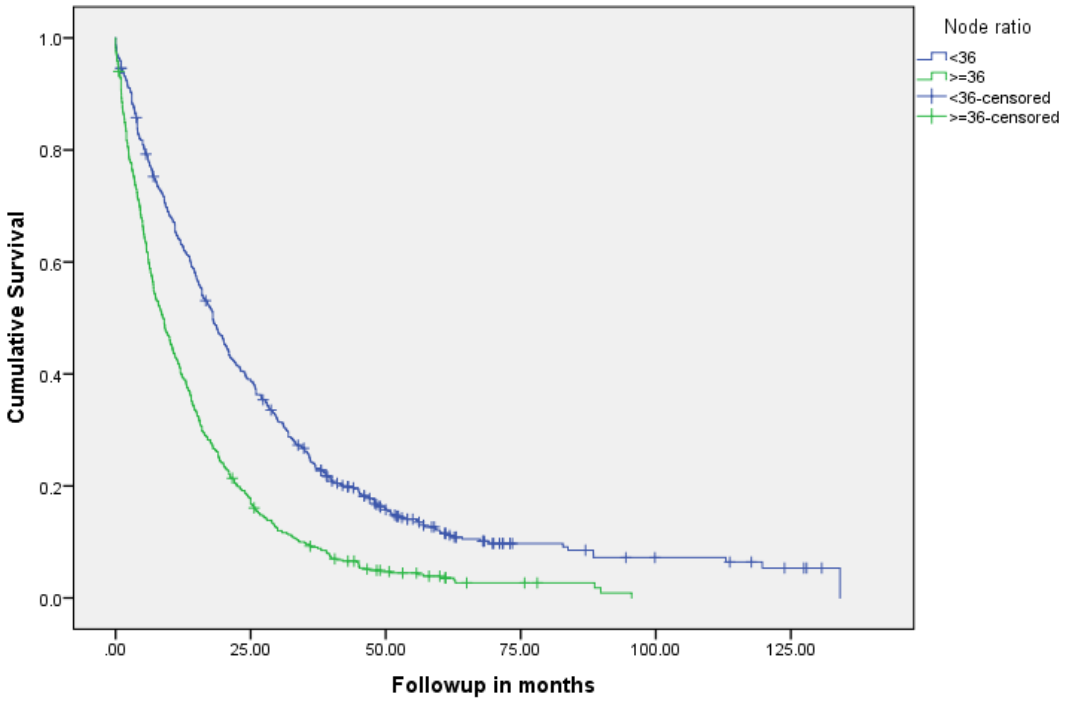


Figure 8.3: Survival of patients with stage IV colorectal cancer based on the ratio of metastatic to examined lymph node (LNR) using a median cutoff value of 0.36 who received chemotherapy.

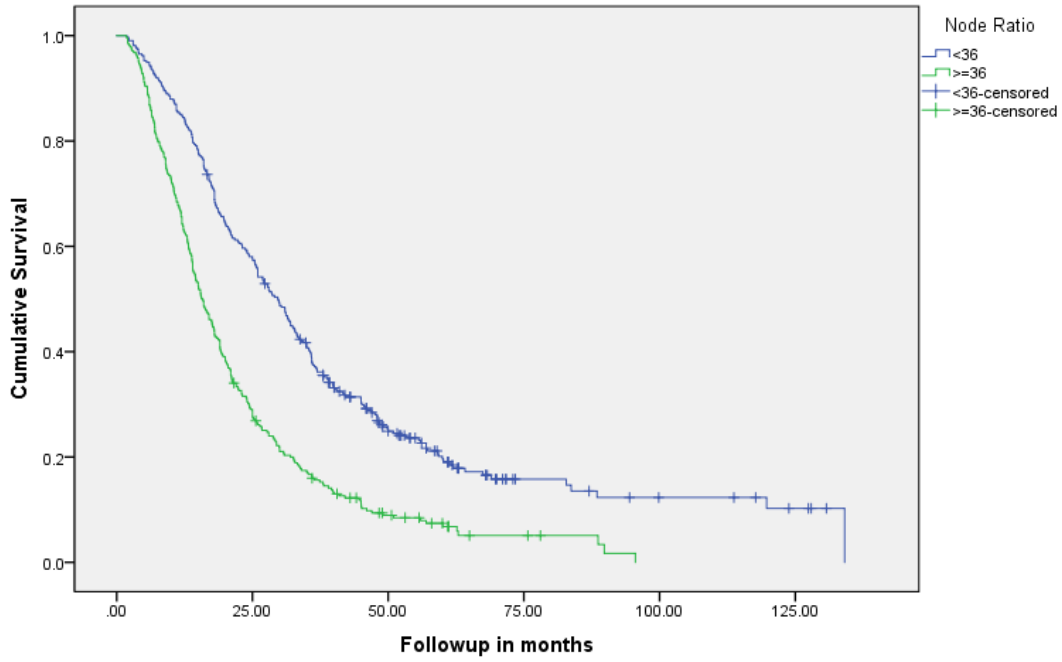
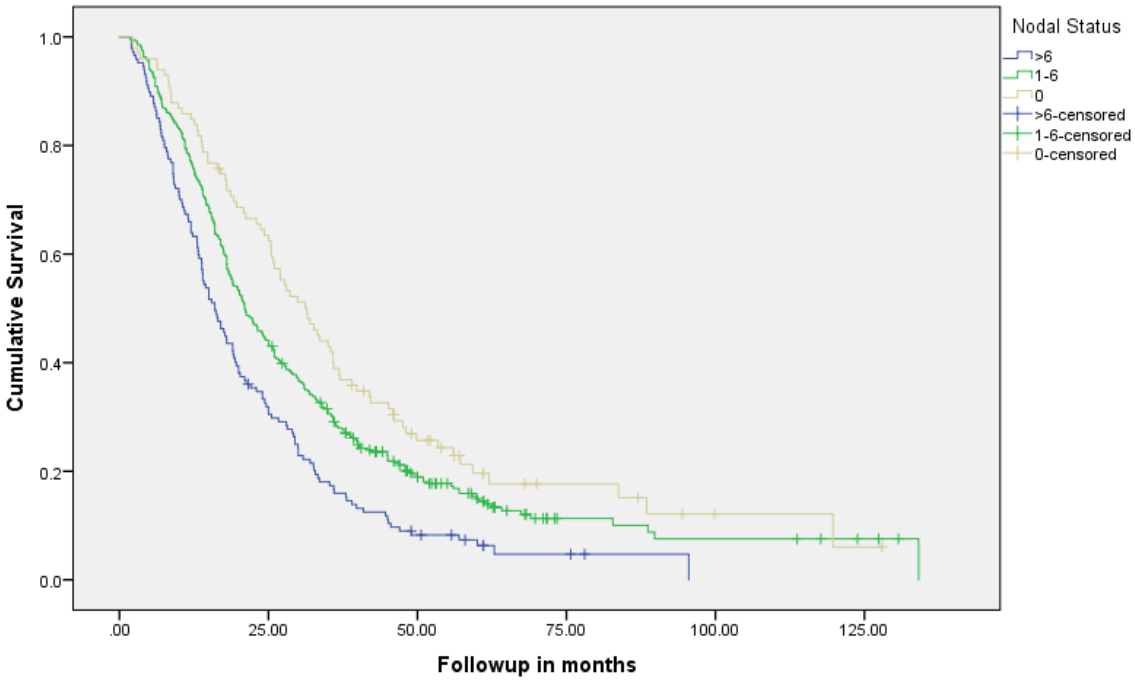


Figure 8.4: Survival of patients with stage IV colorectal cancer based on regional lymph node status.



CHAPTER 9– DISCUSSION AND CONCLUSIONS

Our results favor surgical resection of the primary tumor in patients with stage IV CRC (1-3). The analysis of this large population-based data that spanned over a period of eighteen years demonstrated that the primary tumor resection was associated with better survival and the benefit was independent of other important prognostic factors including age, performance status, comorbid illness, chemotherapy and metastasectomy. The survival benefit of surgery was observed in patients with asymptomatic or minimally symptomatic primary tumor and in patients who were treated with modern chemotherapy (2, 3).

In a cohort of 1378 patients, who were diagnosed with synchronous stage IV CRC from 1992 to 2005, primary tumor resection was associated with 51% relative reduction in mortality (1). In a subgroup of 834 patients with asymptomatic or minimally symptomatic primary tumors, surgical resection of the primary tumor was associated with similar survival benefit with about 53% relative reduction in mortality (2). Of note, less than half of the cohort received chemotherapy and most patients were treated with single agent 5-FU based chemotherapy. Nevertheless, the findings were validated in a second cohort of 569 patients who were diagnosed during the period of 2006-2010 and were treated with modern chemotherapy regimens (3). The study revealed that patients who were treated with combination chemotherapy with or without a biological agent and underwent surgical resection of the primary tumor had better survival compared with the non-resection group. For example, primary tumor resection was associated with 56% relative reduction in mortality during the period of modern chemotherapy. In addition to surgery of the primary tumor, systemic therapy, subsequent line of therapies, metastasectomy, elevated alkaline phosphatase, Grade 3 tumor, leukocytosis, stage IVb disease, and ECOG performance status were correlated with survival.

9.1 Systematic Review and Meta-analysis

We conducted a systemic review and meta-analysis of published literature to determine the survival benefit and complications rates of surgical resection of the primary tumors in patients with stage IV CRC. Previous reviews addressing these questions were mostly restricted to studies performed during the era of single agent chemotherapy or older regimens and included studies with no comparator group (4-6). For example, the review by Eisenberger et al. suggested a potential survival advantage of surgery (4). However, 5 of 12 studies did not have a comparator control group and most studies involved patients treated with single agent 5-FU. An additional review by Scheer et al. that specifically focused on complication rates of the primary tumor did not support surgery (5). Of note, 2 of 7 studies in this review did not have a surgical intervention group. Lastly, Stillwell et al. performed a meta-analysis that favored surgery. Although their review exclusively involved minimally symptomatic patients, 1 of 8 selected

studies did not have a comparator (6). Since the publication of previous systematic reviews additional studies have been reported. Our review exclusively focused on studies with a non-surgical comparator group with a special emphasis on survival and complications rates of subgroup of patients. The review was limited to fifteen retrospective observational studies with their inherent bias. The study period was selected as palliative chemotherapy only became available in the early 1980s. Due to scarcity of resources to translate literatures in other languages we applied English language restriction. Since most relevant studies in CRC management tend to publish in the English literature, we believe that such restriction would have very little if any impact on validity and generalizability of the results.

The review demonstrates a consistent trend favoring non-curative surgical management of the primary tumors in patients with advanced CRC. Overall, 31% relative improvement in survival was noted in the groups treated with surgery. Due to the fact that we did not have individual patients' data about the type of treatment, we used pre-specified criteria for eligible studies to categorize them study using old- versus new-generation therapy. Using these criteria, comparable survival benefit was noted in the studies conducted during the period of new-generation chemotherapy. In agreement with Stillwell et al. meta-analysis, survival advantage was also noted in minimally symptomatic or relatively asymptomatic patients (6). Notably, the pooled estimate of survival revealed considerable inconsistency across the studies. Conceivably, these studies were done in clinically heterogeneous groups with respect to patients population and co-intervention such as age, performance status, comorbid illnesses, disease burden, primary tumor related symptoms, type of systemic therapy and differential rate of metastasectomy. Likewise, considerable variability was noted across the studies design and risk of bias, which suggests methodological diversity. Despite those limitations we opted to report the pool result as the direction of effect was consistent across the studies and subgroups, albeit in different magnitude.

Due to selected reporting and lack of explicit information across the individual studies, examination of heterogeneity with respect to important clinical variables with the exception of underlying symptoms and type of treatment was not feasible. Of note, test for heterogeneity was no longer significant after excluding three studies from the pool estimate which had either larger effect size or were very precise (narrow confidence intervals) suggestive of statistical heterogeneity (7-9). Due to the concern of publication bias, overestimation of the intervention effect relative to the true outcome is quite plausible.

A high postoperative complication can offset the survival benefit related to surgery. Our review was limited by selective reporting of surgical mortality and morbidity across the included studies. Patients with advanced CRC compared with localized disease tend to have an increased mortality rate following primary tumor resection. Although four of nine studies reported no postoperative mortality, in some studies it was not trivial, ranging up to 16%. As anticipated, a higher mortality rate has been noted for emergency surgery (10, 11). The mean primary tumor complication rate including obstruction, perforation, and hemorrhage was 27% but noted to be as high as 63%. A higher complication rate of greater than 50% was mostly noted in the older studies.

Quality of life (QOL) is an important outcome that helps patients and their physicians to choose appropriate treatment. Since the incidence of major intestinal complications related to the primary

tumor such as obstruction, perforation, and hemorrhage, as well as post-operative complications are likely to be associated with a significant adverse effect on QOL, an indirect assessment of QOL can be made by reviewing the surgical and primary tumor complication rates. A surgical intervention with a low complication rate could potentially have a favorable QOL as a result of fewer non-resection interventions, lack of primary tumor related complications and better tolerance to systemic therapy.

A substantial low quality studies, publications bias and selected reporting were the major limitations of the review. Several studies did not provide baseline characteristics of the groups, and others revealed significant imbalance in baseline characteristics of the two groups and did not control for them. Furthermore, only few studies provided detail information about the use and type of systemic therapy in each group making it difficult to assess the relative contribution of resection on outcome. These concerns significantly impact the validity of the observed survival benefit noted in our review and may just reflect selection of younger and healthier patients with good performance status, and low disease burden.

9.2 Cohort Study

Although several studies previously have shown survival benefit of primary tumor resection, validity of survival benefit observed in these studies has been questioned and is believed to be biased by the selection of healthier and younger patients for surgery (12-15). Most studies failed to adjust for performance status and other important clinical and pathological variables. To overcome some of the limitations discussed above, we conducted this well-designed retrospective cohort study. In order to assess the validity of selected studies in the systematic review and meta-analysis we utilized the Newcastle-Ottawa Quality Assessment Scale comprised of nine items grouped in three sections of selection, comparability, and outcome (16). Most were low quality studies with a median score of 5 (range: 4-6). In contrast, our cohort study received one point for each item and scored 9 out of 9.

In agreement with previous studies we noted significant differences in the baseline characteristics between the resection and the control groups. For example, patients who underwent surgery were younger with less disease burden compared with the non-surgical group suggesting a selection bias for the surgical intervention. Nevertheless, when these variables were included in a multivariate model, primary tumor resection remained an important prognostic variable and was associated with significant reduction in mortality when adjusted for age, performance status, comorbid illnesses, chemotherapy, metastasectomy, combination chemotherapy, disease burden and various other important prognostic factors. To our knowledge, the present study is the only study that controlled for all the major known clinical variables to minimize selection bias and has demonstrated survival benefit with primary tumor resection.

9.2.1 Benefit of Surgery in Minimally Symptomatic or Asymptomatic Patients

There is a general agreement that patients with evidence of perforation, significant obstruction, or uncontrolled bleeding should undergo resection of the symptomatic tumor. However, surgical resection of the primary tumor, in patients with asymptomatic or minimally symptomatic disease and otherwise unresectable metastases, is not recommended. In the study cohort, about 60% of patients were asymptomatic or had minimal symptoms related to the primary tumor. These patients had comparable survival benefit with surgical intervention (1-3). Of note, survival differences between the two groups (resection versus non-resection), within the study cohort and various subgroups, were consistently more than 6 months (ranges: 7.6 to 13.6 months). Moreover, the surgical intervention was independently associated with a survival benefit, after controlling for other important prognostic variables. In our validation cohort, patients with relatively asymptomatic primary tumors who underwent surgery and received chemotherapy had median OS of 34 months (95% CI: 24.6-43.4) compared with 21 months (95% CI: 15.6-26.3) if they had symptomatic primary tumor (p=0.006) [3]. Notably, patients with symptomatic primary tumor had 30-day postoperative mortality rates of 8.8% compared with 1.5 % if they had an elective surgery. Emergency surgery has consistently been demonstrated to be an important risk factor for inferior outcome in colorectal surgery and has been associated with a higher 30-day mortality rate (17). We believe that in addition to underlying biology of the disease, the 30-day mortality rate most likely accounted for the differences in survival rates noted between the two groups. Stilwell and others have shown an improvement in the survival of patients with asymptomatic or minimally symptomatic primary tumors, who were treated with palliative resection of primary tumor, with an estimated standardized median difference of 6.0 months (6).

*9.2.2 Benefit of Surgery in Patients Treated with Combination Chemotherapy and Biologi*cs

Modern chemotherapy regimens incorporating novel cytotoxic and biologic agents have been associated with high response rates of 40-50% (18). Although only about 19% of the 1992-2005 cohorts were treated with modern chemotherapy, the magnitude of benefit of surgical intervention was substantially higher in subgroup of patients, who were treated with second-generation and/or second-line chemotherapy.

Furthermore, the 2006-2010 cohort study validated benefit of surgery in patients who were treated with modern chemotherapy. Overall, 57% patients received systemic therapy, of those 91% were treated with combination therapy (FOLFIRI or FOLFOX) and 67% received one or two biological agents. Despite the use of more effective chemotherapy, surgery was associated with 56% relative reduction in mortality. Recent literature also supports survival benefit of surgery of the primary tumor in the era of modern chemotherapy. A retrospective analysis of CAIRO study that compared combination versus sequential chemotherapy demonstrated a significantly better median OS of 16.7 months in patients who underwent surgery compared with 11.4 months with no surgery (HR 0.61, 95%CI:49–0.76) [19]. Likewise, a retrospective analysis of CAIRO II trial that primarily assessed the efficacy of combination of chemotherapy and biologics, demonstrated a superior survival with surgical resection of the primary tumor. In a subgroup of patients who underwent surgical resection of primary tumor, a significantly better median overall survival of 20 months was observed compared with survival of 13.4 months in the non-resection group, (P<0.0001; HR

0.65, 95% CI 0.52–0.80). Furthermore, a pool analysis of four French phase 3 trials involving 850 patients indicated survival benefit of surgery (20). More than two third of patients were treated with FOLFIRI or FOLFOX and about 12% received bevacizumab. The primary tumor resection was an independent predictor of superior survival (HR: 0.63, 95% CI: 0.53-0.75).

In addition, our group' meta-analysis of fifteen observational studies did not reveal a positive interaction between surgery and type of chemotherapy. The HR for survival of the group treated with modern chemotherapy was 0.68 (95% CI: 0.56-0.83) favoring the surgical intervention compared with HR of 0.73 (95% CI: 0.59-0.90) in the group treated with older regimen. However, in this meta-analysis individual patient data regarding type of chemotherapy was not available. Overall, evidence supports comparable benefit of resection of primary tumor in patients treated with modern regimens. Of note, the tests for interactions between the surgical resection of the primary tumor and second-line therapy or disease burden were significant after adjusting for other variables, which suggests that patients who received second-line therapy or who had metastasis confined to one organ or site tend to get greater benefit from surgical removal of the primary tumor.

9.2.3 Postoperative Morbidities and Mortality and Non-surgical Interventions

In the validation study we also evaluated post-operative complications rates in the resection group and non-surgical interventions in the control group. Median duration of hospital stay was 9 days (inter-quartile range: 7-13). Overall, about 24% patients developed post-operative complications. Of note, majority had symptomatic primary tumors. Furthermore, 7% of patients with asymptomatic or minimally symptomatic tumor compared with 15.8% of patients with symptomatic primary tumor developed major postoperative complications including venous thromboembolism, sepsis, wound dehiscence, anastomotic leakage, post-operative bleeding, pelvic abscess and ischemic bowel. The 30-day mortality rate of the group who underwent surgery was 5.4%. Yet again, 1.4% of the patients with asymptomatic or minimally symptomatic disease died within 30 days of surgery compared with 8.8% of the patients with symptomatic primary tumor who underwent urgent or emergent surgeries.

In the non-surgical group 5.2% patients required a stent for their symptoms. In addition, 14.8% patients in the non-resection group developed obstructive symptoms and required a stoma formation (colostomy or ileostomy). Several relatively smaller studies, most of them were designed during the period of modern systemic therapy, assessed the risk of primary tumor complications in patients with non-resection management. These studies reported complications rates related to an intact primary tumor in the range of 3-14% (21-25). About 18% patients in the non-resection group received radiation therapy. No differences were noted in the rates of palliative radiation therapy between the two groups.

9.2.4 Recent Literature

Since the publication of our meta-analysis, primary tumor resection has become one of the key issues in the management of stage IV CRC. Several recent studies have addressed this question in patients with symptomatic or minimally symptomatic tumors (26-29). Ishihara and others retrospectively evaluated 1982 patients with metastatic CRC from 1997 to 2007 (26). Among the whole patient population, primary tumor resection significantly improved survival (HR: 0.46, 95% CI 0.32-0.66). Gresham and others evaluated 517 patients with stage IV CRC (27). Among them, 378 (73 %) patients underwent palliative resection of their primary tumor. Palliative resection was associated with a longer median OS (17.9 vs. 7.9 months) and more favorable adjusted HR for death (0.56, 95 % CI 0.40-0.78). Tarantino and others used the Surveillance, Epidemiology, and End Results (SEER) database from 1998 to 2009 and identified 37,793 patients with stage IV CRC. Of those, 23,004 (60.9%) underwent palliative primary tumor resection. The primary cancer resection was associated with a significantly improved overall survival (HR of death 0.40, 95% CI: 0.39-0.42) [28]. Yun and others assessed 416 patients with asymptomatic unresectable stage IV CRC from the year 2000 to 2008 (29). Among 416 patients, 218 (52.4%) underwent palliative resection of the primary tumor. Their data revealed that palliative resection was not associated with a significantly better survival compared with a non-resection approach.

9.3 Importance of Primary Tumor Pathological Features

The significance of pathological features of primary tumor in patients with stage IV CRC is not known. In the cohort of patients who underwent primary tumor resection, we examined the importance of primary tumor characteristics including the degree of tumor infiltration through the bowel wall (T status), histological grade, number of examined lymph nodes and nodal metastases. Our results suggest that lymph node status and the ratio of metastatic to examined lymph node (LNR) are not only important prognostic factors in the early-stage CRC but also correlate with survival, independent of systemic therapy and other patients- and tumor-related factors, in patients with stage IV CRC (30,31). We noted an inverse relationship between the number of positive regional lymph nodes or LNR and survival. For example, patients with node-negative disease had median OS of 31 months compared with 16 months if they had $\geq$7 regional node were involved. The effect size was larger in patients who were treated with second-generation chemotherapy (FOLFIRI and/or FOLFOX with a biologic). Notably, nodal status and LNR remained important prognostic variables in patients who underwent metastasectomy and independently correlated with survival.

In addition to the nodal status, the depth of local tumor invasion (T status) was correlated with survival. Since majority of the patients with stage IV CRC had T3 or T4, T status was examined as a continuous variable. The depth of local tumor invasion is a well-known prognostic factor, both in node-positive and node-negative early-stage CRC (32). However, relative to regional lymph node status, the association between T status and lymph node was weak. In addition, in this group of patients who underwent surgical resection of the primary tumor, chemotherapy, metastasectomy, performance status, stage IVb disease, tumor location, leukocytosis, and abnormal alkaline phosphatase, CEA, and bilirubin levels were correlated with survival.

The mechanisms underlying the relationship between the regional node status and survival in stage IV CRC is not known. Lymph node status is most likely a surrogate marker of the underlying tumor biology and host response to the disease. Unlike early-stage CRC, where LNR and nodal status reflect accurate tumor staging, more efficacious surgical intervention, and superior quality of pathology service and correlate with better survival, other factors may account for difference in survival in stage IV CRC. For example, a greater host immune response among patients with a larger negative lymph node count, or other unknown underlying molecular/biological characteristics of tumor may account for the difference in survival.

9.4 Prognostic Factors in Stage IV Colorectal Cancer

A variety of clinical parameters such as age, performance status, WBC count, hemoglobin, serum albumin, alkaline phosphatase, CEA, pathological grading or localization of the primary tumor have been identified as prognostic markers in patients with stage IV CRC (33-36). Our data is one of the largest data sets that included patients-related factors, tumor-related factors, baseline laboratory values and various interventions in multivariate models. Our study revealed that in addition to surgery of the primary tumor, systemic therapy, subsequent-line of therapy, metastasectomy, elevated alkaline phosphatase, low albumin, Grade 3 tumor, leukocytosis, stage IVb disease, and ECOG performance status were correlated with survival in patients with stage IV CRC.

Systemic therapy is the most important prognostic variables in stage IV CRC and has been associated with significant improvement in the outcomes of patients with metastatic CRC. A randomized trial demonstrated that patients who received 5-fluorouracil (5-FU) based chemotherapy had median overall survival of 11 months compared with 5 months with best supportive care alone (37).With the introduction of 5-FU, a fluoropyrimidine, median overall survival of patients with stage IV CRC improved to approximately 10-12 months. For many decades, 5-FU remained the sole active agent used in the management of advanced CRC. In the later part of 1980s, the addition of biomodulator leucovorin (LV) to 5-FU resulted in modest improvement in response rate and overall survival (38). A decade later both irinotecan and oxaliplatin demonstrated efficacy as second-line treatments, and subsequently approved as first-line therapies for metastatic CRC with improvement in median overall survival to 15-20 months (39-42). Biological therapies such as cetuximab and bevacizumab bring average survival lengths to approximately 20-30 months (43, 44). With the availability of novel agents in the management of advanced CRC, we noted approximately 25% increase in the use of chemotherapy. Patients treated with curative intention or underwent resection of primary tumor were more likely to received chemotherapy. A Canadian study also demonstrated similar findings (45). Between 2003 and 2004 (pre-bevacizumab era) and 2006 (bevacizumab era), the proportion of patients treated with systemic therapy for stage IV CRC significantly increased from 61.1% to 67.6%.

It is known that survival of patients with stage IV CRC is better if they are exposed to all available active therapeutic agents during the course of their disease (46). Effective salvage therapies (second- or third-line therapies) have a significant impact on patient outcomes and have been associated with improvement in survival (47, 48). Our results showed that the patients who received FOLFIRI and FOLFOX in combination with a biologic agent and underwent resection of the primary tumor had median survival of 35 months (95% CI: 30-40). Furthermore, patients with

KRAS wild tumor who received FOLFIRI & FOLFOX in combination with bevacizumab and subsequently were treated with an anti-EGFR monoclonal antibody had a median OS of 39 months (95%CI: 25.1-52.9) [3]. Due to presence of multicollinearity between various lines of chemotherapy and the type of regimens, these variables were not fitted together in the final model. Nevertheless, secondary analyses using chemotherapy regimens and biological agents as opposed to the subsequent-line of therapies, underscored their prognostic importance. Both combination of chemotherapy (HR: 0.67, 95%CI: 0.52-0.87) and biological agents (HR: 0.60, 95%CI: 0.45-0.78) were independently correlated with superior survival. Furthermore, surgery of the primary tumor in the model using various systemic therapy regimens was independently correlated with survival.

Although our results suggest that chemotherapy utilization is increasing over time, a substantial number of patients for several reasons did not receive chemotherapy. Future research exploring the correlation between the use of chemotherapy and biologics and various socio-economic determinants is important to improve the outcomes of patients with metastatic CRC. Saskatchewan is a geographically large province with a population of about 1.1 million. We plan to validate our findings in 2006-10 cohort and explore relationship between the travel distance to the cancer center and the use of chemotherapy in patients with stage IV CRC.

In addition to systemic therapy and primary tumor resection, metastasectomy was associated with better survival. The presence of systemic metastases is a poor prognostic markers in cancer patients with a very short survival in most gastrointestinal malignancies. Nevertheless, limited metastatic disease in CRC, involving the liver or lungs, does not mean that long-term remission cannot be achieved. Surgical resection is the only potentially curative option for selected patients with limited liver or lung metastases. Although randomized trials have not been conducted, long term survival of about 30-40% reported in retrospective observational studies have led to the acceptance of aggressive metastasectomy in patients with limited lung and/or liver metastases (49-52). The liver is the dominant metastatic site in patients with CRC and 80-90% developed unresectable liver metastases. With the availability of novel chemotherapy and targeted agents, about 10-20% patients with initially unresectable or borderline resectable metastatic liver disease can have significant response to treatment and are able to undergo resection of the metastases. Comparable to liver metastasectomy, patients who underwent pulmonary metastasectomy along with removal of the primary tumor had five- and ten-year survival rates of about 35-55% and 20-30%, respectively (53-55). Since patients who undergo metastasectomy have potential to achieve long term survival, a secondary analysis was performed after excluding the patients who underwent metastasectomy. Despite the exclusion of patients with good prognosis, in a multivariate analysis, removal of the primary tumor was associated with 52% relative reduction in mortality.

Among various prognostic variables, elevated alkaline phosphatase, low albumin, leukocytosis, Grade 3 tumors, stage IVb disease, and ECOG performance status were correlated with inferior survival in patients with stage IV CRC. Alkaline phosphatase (ALP) comprises a group of enzymes that catalyze the hydrolysis of phosphate esters and is mainly derived from the liver, bones, and in lesser amounts from intestines, kidneys, and leukocytes (56,57). Serum ALP levels are frequently elevated in patients with metastatic CRC (56). Our data revealed that patients who received combination of chemotherapy and had elevated ALP had median OS of 17 (14.8-19.2) months compared with 27 (22.5-31.5) months if they had normal ALP (<0.001). After adjusting for other

important covariates baseline abnormal ALP level was associated with 50% relative increase in mortality.

In addition to ALP, baseline low serum albumin correlated with inferior survival. Serum albumin provides a simple method of estimating visceral protein function. Malnutrition and inflammation suppress albumin synthesis (58). Low serum albumin is one of the surrogate markers of malnutrition in patients with advanced cancer. Several observational studies have suggested that low serum albumin is associated with higher mortality from cancer (58). Malnutrition in patients with advanced cancer is not uncommon and results from underlying cancer, the host response to the cancer, and anticancer therapies. Malnutrition has been associated with an increased risk of chemotherapy-related toxicity, decreased response to treatment, poor quality of life, and an inferior survival (58, 59). Likewise, the histologic grade of a tumor provides prognostic information. Poorly-differentiated tumors are known to pursue a more aggressive course than their well-differentiated counterparts (60). Patients with poorly-differentiated stage IV CRC had about 33% increased risk of mortality.

Our data also revealed that baseline leukocytosis in patients with stage IV CRC was associated with poor prognosis. Leukocytosis has been demonstrated to be associated with increased mortality in cancer patients (61-63). For example, Connolly and others have demonstrated that elevated WBC has been strongly associated with an increased risk of venous thromboembolism and mortality in cancer patients receiving systemic chemotherapy. Leukocytosis may be a marker of an underlying process such as more aggressive malignancy, major co-morbidities, inflammation, or leukocytes may be actively involved in disease progression and cancer-associated thrombosis (64). It has been shown that tissue factor and VEGF levels in leukocytes from cancer patients is many fold higher than in leukocytes from normal controls (64, 65). It is plausible that leukocytes may directly contribute to disease progression through release of tissue factor and VEGF. Furthermore, cytokines secreted by leukocyte may promote a microenvironment that supports thrombus generation, tumor growth, metastasis, and chemotherapy resistance (66, 67).

In agreement with previous observation, patients with more than one metastatic sites or stage IVb disease had inferior survival. There is evidence that both the total number of metastases and the location of the metastatic disease are associated with prognosis (68, 69). However, among patients with a large tumor burden, prognostic significance of anatomic location is relatively less important (68). In seventh edition of American Joint Committee on Cancer (AJCC) cancer staging manual, metastasis to only one site such as liver, lung, ovary, or non-regional node has been classified as M1a disease or stage IVa cancer whereas metastasis to multiple sites or to the peritoneum has been classified as M1b or stage IVb cancer (70).

As expected significantly more patients were diagnosed with a rectal or recto-sigmoid tumor, in the control group. Despites that, for reason not clear, patients with rectal or recto-sigmoid tumors compared with more proximal tumor had better survival. Frerrand and colleagues reported a similar observation in their retrospective analysis of FFCD 9601 trial (71). These differences in patient survival were maintained after exclusion of patients with rectal primary.

With few exceptions, in most advanced solid tumors, poor performance status correlates with inferior survival and in many cases poor response to chemotherapy (72). Hence, there is a general agreement that patients with advanced solid tumors with a poor performance status would gain little benefit from chemotherapy. Data on patients with advanced CRC and poor performance status are scant. Clinical trials often exclude patients with ECOG performance status of ≥2 or with limited life expectancy. In our study cohort, patients with poor performance status, who received chemotherapy, had significantly lower overall survival compared with patients with good performance status. The modification in the chemotherapeutic regimen and dose reduction may reduce major complications in patients with borderline performance status. In addition, treatment should be started as soon as possible before the performance status further deteriorates. It is not known if access to more effective anti-cancer therapy, better anti-emetics, and growth factors support improve outcomes of such patients.

We also evaluated prognostic significance of area level variables including household income, family income, age dependency ratio, unemployment rate, aboriginal and minority population, high school certificate, single parenthood, and socio-economic Factor Index 2 (SAFEI2) in stage IV CRC. For income, unemployment rates and SAFEI2, the STATA software could not calculate numerical derivatives. For the other variables relationship was not significant (**Appendix 11**). We believe that absence of relationship is most likely due to small sample resulting in fewer numbers of observations in the census subdivisions rather than a true finding.

9.5 Potential Mechanisms of Survival Benefit of Surgery

The underlying mechanisms that resulted in better outcomes of the patients treated with surgery remains speculative. A benefit for primary tumor resection in stage IV renal cell cancer has been demonstrated in the two randomized controlled trials (73, 74). For example, radical nephrectomy prior to systemic therapy was associated with significantly better overall survival of 17 months in the surgical group compared with 7 months in the controls (73). Furthermore, observational studies support primary tumor resection in women with metastatic breast cancer (75). Non-curative resection of the primary tumor in patients with advanced cancer may prevent local tumor complications and improve disease control by reducing the tumor bulk and tolerance to systemic therapy. Furthermore, there is evidence for the genetic variation between the primary tumors and metastases (76). Removal of the primary tumor may result in a decreased burden of chemotactic cytokines and tumor-promoting factors which are produced by colorectal cancers, and regulate tumor cells growth and metastasis (77, 78). In addition, alteration in immune response following surgery, with predominant T helper 1 response than one with a substantial T helper 2 component may contribute to a better outcome (79).

It has been shown that resection of the primary tumor may eliminate tumor-induced immunosuppression, primary tumor cells homing and seeding to distant sites, and may remove a source of potentially chemo-resistant cell lines (80-82). Tumor-induced immunosuppression is a fundamental mechanism, which allows malignant cells to escape immune destruction. Tumor cells are known to synthesize and secrete several immunosuppressive factors. For example, transforming growth factor β inhibits $CD8^+$ effector T cells and Th1 $CD4^+$ T cells, thereby suppressing T-cell-mediated antitumor immunity (80, 83). It is possible that patients with bulky

primary tumors are profoundly immunosuppressed and primary tumor removal reverses immune suppression even in the presence of extensive metastatic disease.

9.6 Strengths and Weaknesses

There are several potential strengths and weakness of our study which are outlined below.

9.6.1 Strengths

- To our knowledge this is the only large population based cohort study that examined several patients-related factors (age, co-morbid illness, performance status, etc.), cancer-related factors (site, grade, disease burden, symptoms, etc.), laboratory values (leukocyte, albumin, alkaline phosphatase, CEA, etc.), and interventions (chemotherapy, biologics, metastasectomy, radiation, etc.) in a multivariate model and demonstrated survival benefit of primary tumor resection independent of the other variables.
- Individual patients' data were obtained in all cases. In order to avoid erroneous exclusion of eligible patients, more than 10,000 individual records of patients with all stages CRC (stage I-IV) were retrieved and patients (stage IV adenocarcinoma of colon and rectum) were selected based on inclusion and exclusion criteria.
- Being a population-based study the study cohort was true representative of patients with stage IV CRC in the community. All patients had a complete follow-up and no subject was lost to follow-up to introduce bias.
- The study population was heterogeneous and benefit of surgery was demonstrated in all patients groups (symptomatic versus asymptomatic or with minimally symptomatic primary tumor and patients who were treated with single agent chemotherapy versus those who received combination chemotherapy and biologics). Hence, our results are generalizable to the other people with stage IV CRC.
- The study period spanned about twenty years and benefit of surgery was demonstrated both in the early and the later time periods.

9.6.2 Limitations

- Due to lack of randomization, imbalance of unknown prognostic variables between resection and non-resection groups cannot be eliminated.
- Data was obtained retrospectively and the medical records were not designed for the study purpose.
- In the study cohort we do not have information about BRAF mutation which has been reported in about 5-11% stage IV CRC and is an important prognostic biomarker (84). It is not known if differential distributions of BRAF mutation in the study groups have accounted for difference in survival.
- In addition, disease burden was not measured in patients with single versus multiple site metastases. Hence, better survival secondary to selection of patients with low disease burden, who have better prognosis, cannot be eliminated.
- Although the prognostic role of area-level variables was assessed in a subgroup of patients, our study lacks individual information on social determinants of health.

9.7 Future Direction

Cancer is one of the leading causes of death globally. According to the Canadian Cancer Society, 40% of males and 45% of females are expected to develop cancer during their lifetime and one in four Canadians will die from cancer (85). With recent advancement in cancer management and research, the outcomes of cancer patients, specifically in the developed countries have improved. However, over the past decade, the cost of cancer care has exponentially gone up (86, 87). For example, the drugs associated with cancer care are estimated to cost approximately $40 billion USD per year globally (88). In 2010, $14 billion was spent in the United States on management of colorectal cancer (89). Monoclonal antibodies are an important component of systemic therapy in patients with stage IV CRC. For example, bevacizumab, a monoclonal antibody against the VEGF A, is commonly used in combination with chemotherapy in stage IV CRC (90, 91). It costs about $4000-5000 USD per dose for an average weight person. Goldstein et al. have estimated that bevacizumab provides minimal incremental benefit at high incremental cost per quality-adjusted life year (QALY) in stage IV CRC (92). In their economical analyses, bevacizumab in first-line therapy provided an additional 0.10 QALYs (0.14 life-years) at a cost of $59,361. The incremental cost-effectiveness ratio was $571,240 per QALY. Likewise, anti-EGFR monoclonal antibodies cetuximab or panitumumab have demonstrated efficacy in patients with RAS wild metastatic CRC (93, 94). However, these monoclonal antibodies cost about $ 7500 to 10000 USD per dose for an average weight person and compared with best supportive care are not found to be cost-effective (95,96).

The current study revealed that patients with stage IV CRC with symptomatic or asymptomatic or minimally symptomatic primary tumor who underwent surgery had better survival with overall 50-60% relative reduction in mortality after adjustment for older age, comorbid illness, poor performance status, disease burden, chemotherapy, and metastasectomy. A larger benefit of surgery was noted in patients with stage IVA disease or who received subsequent lines of therapies. The group of patients who underwent surgical resection of primary tumor during the period of modern chemotherapy had 30-day postoperative mortality rate of about 5%. However, patients who underwent elective surgery and had asymptomatic or minimally symptomatic primary tumors had operative mortality rate of only 1.5 % (1-3). The major postoperative complications rate was 11.8%; 7% in asymptomatic or minimally symptomatic compared with 15.8% in patients with symptomatic primary tumor (p=0.01).

Based on the result of ours and others, two randomized controlled trials in Europe have been designed to confirm survival benefit of resection of the primary tumor in stage IV CRC (97,98). The SYNCHRNOUS trial is comparing primary tumor resection to no surgery in patients with colon cancer and synchronous metastases who are not amenable to curative therapy (97). The CAIRO 4 trial is evaluating this question in patients with stage IV colon and rectal cancer (98). If the magnitude of survival benefits is confirmed in these future randomized studies, surgical resection of the primary tumor could potentially be a more cost effective intervention in the management of metastatic CRC.

9.7.1 The SYNCHRONOUS Trial

The SYNCHRONOUS trial will assess the efficacy and safety of primary tumor resection in patients with stage IV CRC (97). The primary objective of the trial is to investigate, if primary tumor resection prolongs survival of patients with colon cancer and synchronous metastases, not amenable to curative therapy.

It is a multicentre, randomized controlled, superiority trial with a two-group parallel design. Colon cancer patients with synchronous unresectable metastases are eligible for inclusion. Exclusion criteria include symptomatic primary tumor, inability to tolerate surgery or chemotherapy and history of another primary cancer. The SYNCHRONOUS trial will be conducted as an intergroup trial of the Study Centre of the German Surgical Society (SDGC), the German Surgical Network of Clinical Studies (CHIR-Net) together with the Colorectal Study Group of the Arbeitsgemeinschaft Internistische Onkologie (AIO) of the German Cancer Society and the Association of Certified Intestinal Centers. Patient will be recruited at more than 60 trial centers in Europe.

Patients in the experimental arm will undergo primary tumor resection prior to commencement of systemic chemotherapy. Surgery will be performed within 14 days of randomization. Systemic therapy will be started within 8 weeks after surgery. Patients in the control arm will receive chemotherapy and treatment will start within 14 days of randomization. The choice for the chemotherapy will be at discretion of the treating oncologist at each participating institution. Patients who become candidates for curative resection may receive further treatment with curative intent.

The primary hypothesis is that resection of the primary tumor prolongs survival from 20 to 26 months compared to systemic therapy without prior tumor resection. To detect a hazard ratio of 1.3 with a two-sided test for treatment effect at a significance level of 5% within a Cox model without covariates with a power of 85%, 694 patients (347 per group) have to be included in the analysis, leading to a total number of events of 522. The accrual period is projected to be 24 months and the follow-up period will be 36 months.

9.7.2 The CAIRO Trial

The CAIRO trial is a multicenter, randomized phase III Dutch trial which is evaluating the clinical benefit of primary tumor resection in patients with synchronous unresectable metastatic colon cancer (98). Unlike SYNCHRONOUS trial patients with colon or rectal cancer are included in this study. Patients with synchronous metastatic colon cancer with asymptomatic or minimally symptomatic primary tumor will be randomized 1:1 between systemic treatment and primary tumor resection followed by systemic treatment.

In order to demonstrate a clinically relevant increase of 6 months of the median overall survival in the experimental arm, a total of 218 deaths will be required (80% power, significance level 0.05). With a recruitment rate of 12 patients per month, an accrual period of 30 months and a follow-up period of 8 months, a total of 360 patients will be required in order to detect a difference in median overall survival of 13 versus 19 months with a power of 80%.

In the control arm first-line fluoropyrimidine-based chemotherapy with bevacizumab will be initiated within 4 weeks of randomization, followed by salvage therapy on progression at the discretion of the treating investigator. Surgery of primary tumor in this group will be performed only when indicated by local signs or symptoms. In the experimental arm surgery will be performed within 4 weeks of randomization followed by fluoropyrimidine-based chemotherapy with bevacizumab until progression or unacceptable toxicity, followed by salvage therapy on progression at the discretion of the local investigator.

9.7.3 Relationship between the Primary Tumor and Host Immune Response

The immune systems of cancer patients are able to recognize cancer specific antigens (99,100). A strong and a predominant cytotoxic T lymphocyte, Th1 response against cancer cells may keep the disease under control while tumor progression may occur with a predominant Th2 component that down-regulates the Th1 response (101,102). This phenomenon has been referred to as *Th2-Skewing Hypothesis of Tumor Escape*. Of note, the Th1/Th2 phenotype of an immune response to an antigen can be inferred from the relative prevalence of IgG isotypes among the antibodies specific for this antigen. A predominant Th1 response correlates with a low IgG_1/IgG_2 ratio, whereas a predominant Th2 response correlates with a high IgG_1/IgG_2 ratio. This indirect assessment of the Th1/Th2 immune response has been referred as the *IgG isotype methodology* (101).

Although host factors are critical in regulating cancer, the role of immune response in advanced colorectal cancer (CRC) is less clear. Our research group has developed an ELISA assays for the monitoring of immune responses against in patients with metastatic CRC. Our preliminary results showed that patients with metastatic CRC had elevated IgG1/IgG2 ratio compared with healthy control and the elevated ratios correlated with the disease progression (79). This work could be a base for future studies to explore the potential mechanisms of survival benefit of primary tumor resection and to determine if host immune responses (Th1 versus Th2) play a role in outcomes following primary tumor resection.

9.8 Conclusions

In summary, this well-designed population-based cohort study, with minimal selection and information biases, and appropriate follow up supports surgical resection of the primary tumor in patients with stage IV CRC, independent of other important prognostic factors. The benefit is greater in patients with limited burden of the disease or if they received subsequent line of therapies. Patients who are treated with combination therapy or who have minimally symptomatic primary tumor experienced comparable benefit. In surgically treated patients pathological characteristic of the primary tumor such as nodal status, lymph node ratio, and tumor depth correlate with prognosis.

The results warrant a well-designed randomized clinical trial to confirm survival benefit of surgery. Two randomized controlled trials in Europe are currently enrolling patients to confirm benefit of surgery (85, 86). We hope that the both trials will complete the planned accrual and will be able to answer this important question in the management of stage IV CRC.

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APPENDIX A: SEARCH STRATEGY

Question to be Answered:

Should palliative resection of the primary tumor be performed in patients with advanced colorectal cancer? A Systematic Review

Bibliographic Databases to be Searched:

MEDLINE
EMBASE
CENTRAL
In addition, grey literature (the American Society of Clinical Oncology and the European Society of Medical Oncology guidelines, education books, the National Comprehensive Cancer Network guideline) was reviewed for relevant studies.

Search Terms for the Major Concepts in the Question:

Advanced colorectal cancer term was divided into "colorectal cancer" AND "advanced"
Colorectal cancer
colon cancer/colon carcinoma
colon tumor/large intestine cancer
rectal cancer/ rectal neoplasm/rectum cancer
sigmoid carcinoma/sigmoid neoplasms
colorectal neoplasm/colorectal cancer/colorectal carcinoma
colon neoplasm/colonic neoplasms
sigmoid colon cancer
cecal cancer/cecum carcinoma
colorectal neoplasms, hereditary nonpolyposis

Advanced
stage IV or stage 4 or stage four or metastatic or advanced cancer

Surgery
general surgery or colon surgery or rectal surgery
The Boolean operator "AND" was used to combine these headings to maximize precision while maintaining high recall.

Terms for Appropriate Study Design (Evidence)

Due to the concern of lack of controlled trials addressing this question, no study design restriction was applied. All the following study designs were eligible for review

- Randomized controlled trial
- Controlled clinical trial
- Cohort studies (prospective and retrospective)
- Case-control studies

Restriction to the Search

- Publication status: Full published articles (to avoid studies with limited information)
- Human studies
- 1980 to 2012 (The study period was chosen as palliative chemotherapy become available in early 80s).
- English language

Inclusion & Exclusion Criteria

Inclusion Criteria

- Study Population
  - Patients with advanced adenocarcinoma of colon and rectum
- Intervention
  - Surgical resection of the primary tumor
- Control group
  - no surgery
- Outcome of interest
  - Primary outcome of interest: Overall survival
  - Secondary outcomes of interest: Surgical mortality & morbidity, complications of primary tumor, nonsurgical intervention in the control group, rate of subsequent metastasectomy
- Research design
  - Randomized controlled trial, cohort study (prospective &retrospective), case control

Exclusion Criteria

- Patients with small cell carcinoma, gastrointestinal stromal tumor (GIST), lymphoma, melanoma, anal canal cancer, melanoma and sarcoma of colon and rectum.
- Patients with advanced colorectal cancer who underwent surgery with curative intention
- Patients who had palliative bypass surgery (colostomy formation) or stent placement with an intact primary tumor.
- Patients who received palliative radiation therapy to the primary tumor and did not have surgical resection of the primary tumor

Subgroups

- Patients with minimal or relatively asymptomatic primary tumor
- Patients who were treated with second- and third-generation chemotherapy

Search Strategy

Literature search was conducted by consulting a health science librarian at the U of S. The search was performed in three stages.
In the first stage the MEDLINE, & EMBASE databases were searched for relevant studies. The University of Saskatchewan Ovid interface was used for the MEDLINE (1946-current) and EMBASE (1947-current).

- All relevant studies were identified using the first 3 components of the PICO format.
- Studies comparing survival of patients with stage IV colorectal cancer who underwent primary tumor resection (study group) with patients who did not have surgery were included.
- Only studies with histologically documented adenocarcinoma of colon and rectum and evidence of metastases were included. Studies involving patients with other histological diagnosis including small cell carcinoma, gastrointestinal stromal tumor, lymphoma, melanoma, anal canal cancer, melanoma and sarcoma were excluded.

Following concepts were used:

1. Advanced colorectal cancer
2. Surgery

A pilot search was performed and various key words and controlled vocabulary (for different concepts) were used utilizing 'explode' and 'focus' (for controlled vocabulary) in various combination. Because the use of 'explode' revealed mostly irrelevant articles, after consulting a librarian, in the final search 'explode' and 'focus' were not used. Likewise, when the key word "advanced colorectal cancer" with its synonyms was used, only small number of articles were retrieved. In order to increase the search sensitivity, the term "Advanced colorectal cancer" was broken into to the terms "advanced" AND "colorectal cancer".

- Following keywords, synonyms, and controlled vocabulary (MESH & EMTREE) were used
  - ''colorectal cancer'' or ''colon cancer'' or ''rectal cancer'' or '' colorectal neoplasm'' or "colon neoplasm" or "rectal neoplasm" please see the search terms above for detail)
  - "advanced " or "stage IV" or "stage 4" or "stage four" or "metastatic:
  - "surgery" or "colorectal surgery" or ''palliative surgery" or "palliative surgery" or "surgical removal"
- The three sets of terms were subsequently join together with the 'AND' operator.
- Studies were selected by using pre-specified criteria with restriction to the publication dates from 1980 onward, the English language, and human studies.
- The title and abstract of the searched articles were reviewed to identify relevant studies. In addition, using 'similar study' further studies were identified and exported to the Refwork.
- A hand search was performed and the reference lists of the identified articles were reviewed to identify additional articles for assessment. In addition, PubMed search was done to eliminate any recent articles using different key words.

In the second stage, the CENTRAL was searched using the term "colorectal cancer" or "colon cancer" or rectal cancer" or "colorectal neoplasms" and "surgery". In order to increase the search sensitivity, the term "advanced" or "stage IV" was avoided.

In the third and final stage of search, the grey literature including the education material from scientific proceedings and current practice guidelines for the management of colon and rectal cancer by the American Society of Clinical Oncology [ASCO], the European Society of Medical Oncology [ESMO]) and the National Comprehensive Cancer Network (NCCN) was reviewed. Citation index was used to identify relevant articles in that subject.

APPENDIX B: SEARCH TERMS

Database: Ovid MEDLINE(R) <1946 to February Week 4 2012>
Search Strategy:
---

1. Colonic Neoplasms/
2. Colorectal Neoplasms/
3. Rectal Neoplasms/
4. cecal neoplasms/ or colonic neoplasms/ or sigmoid neoplasms/ or colorectal neoplasms, hereditary nonpolyposis/
5. Colorectal cancer.mp.
6. Colon cancer.mp.
7. Rectal cancer.mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Advanced cancer.mp.
10. advanced.mp.
11. Stage IV.mp.
12. Stage four.mp.
13. metastatic.mp.
14. 9 or 10 or 11 or 12 or 13
15. 8 and 14 (
16. Colorectal Surgery/
17. surg.mp.
18. Exp General Surgery/
19. 16 or 17 or 18
20. removal.mp.
21. 19 or 20
22. 15 and 21
23. limit 22 to (English language and humans and yr="1980 -Current")
24. "Palliative surgery". Mp.
25. 21 or 24
26. 15 and 25
27. "Palliative resection". Mp.
28. 25 or 27
29. 15 and 28
30. limit 29 to (English language and humans and yr="1980 -Current")
31. Find similar to Elective palliative resection of incurable stage IV colorectal cancer: who really benefits from it?
32. Find similar to the role of primary tumour resection in patients with stage IV colorectal cancer.
33. Find similar to Surgery of the primary in stage IV colorectal cancer with unresectable metastases.
34. from 33 keep 9-10
35. Find similar to Elective bowel resection for incurable stage IV colorectal cancer: prognostic variables for asymptomatic patients.

Database: Embase Classic+Embase <1947 to 2012 February 05>
Search Strategy:
---

1. colon cancer/ or colon tumor/ or large intestine cancer/
2. colon carcinoma/ or colorectal cancer/ or colorectal carcinoma/ or sigmoid carcinoma/
3. sigmoid carcinoma/
4. cecum carcinoma/
5. rectum cancer/
6. rectum carcinoma/
7. 1 or 2 or 3 or 4 or 5 or 6
8. "Stage IV".mp.
9. "Stage 4".mp.
10. advanced cancer/
11. metastatic.mp.
12. Stage four.mp.
13. 8 or 9 or 10 or 11 or 12
14. 7 and 13
15. "Palliative surgery". Mp.
16. "Palliative resection". Mp.
17. colon surgery/ or colorectal surgery/ or rectum surgery/
18. "Surgical removal". Mp.
19. 15 or 16 or 17 or 18
20. 14 and 19
21. limit 20 to (human and English language and yr="1980 -Current")
22. from 21 keep 11,31,35,51,67,114,118,139,146,193,217-218,269,385,439,446
23. find similar to Elective bowel resection for incurable stage IV colorectal cancer: Prognostic variables for asymptomatic patients
24. Find similar to colorectal cancer with multiple metastases: Is palliative surgery needed?
25. find similar to Surgery of the primary in stage IV colorectal cancer with unresectable metastases
26. find similar to Intestinal complications after palliative treatment for asymptomatic patients with unresectable stage IV colorectal cancer
27. Find similar to How Aggressive Should We Be in Patients with Stage IV Colorectal Cancer?
28. Find similar to Is there a survival advantage for elective primary tumor resection in asymptomatic patients with incurable stage IV colorectal cancer?

APPENDIX C: FULL TEXT SCREENING FORM*

Reviewer:	☐ SA ☐ RKS
Reference ID:	
Last name of the first author:	
Title:	
Journal:	
Date of publication	D/M/Y

Criteria for exclusion	
Study design	ANY of the following ☐ No independent control group (e.g. case report or case series) ☐ No comparator group ☐ Conference abstract ☐ Other type of publication (i.e. not a clinical study or review)
Population	ANY of the following ☐ Not patients with colorectal cancer ☐ Patients with TNM stage 1, 2, 3 colorectal cancer ☐ Patients with colorectal cancer of histopathology other than adenocarcinoma (melanoma, GIST, lymphoma, small cell carcinoma) ☐ Patients with colorectal cancer who had resection of primary tumor with curative intent
Intervention	ANY of the following ☐ procedures other than resection of primary tumor (colostomy formation, stent, radiation)
Comparator	☐ Non resection surgery ☐ curative surgery

Criteria for inclusion	
Study design	☐ Randomized controlled trial ☐ non-randomized trial ☐ Cohort study ☐ Case control ☐ Review**
Population	☐ Patients with advanced colorectal adenocarcinoma
Interventions in experimental group	ANY of the following ☐ Surgical resection of the primary tumor

☐ **TO BE INCLUDED**
☐ FURTHER ACTION REQUIRED What action:

☐ **TO BE EXCLUDED** What action:
☐ FURTHER ACTION REQUIRED (i.e. duplicate)

Additional comments:

***** *The two coauthors using the PICO format developed a full text screening format. Prior to development of form, both authors randomly screened the database searched for the systematic review. A previous full text screening form template was used for this purpose. Based on a priori knowledge, inclusion and exclusion criteria were developed. Human, the English language, and time period (1980- present) restrictions were applied in the search databases.*
*** Reviews were included for hand search of citations and identification of other studies.*

APPENDIX D - DATA ABSTRACTION FORM SURGICAL MANAGEMENT VS. CONSERVATIVE TREATMENT

Study Characteristics

1. **Journal:**

2. **Last name of First Author:**

3. **Year of publication:**

4. **Country/countries where study took place**:

5. **Type of Center:**
   Multicenter Single Center

6. **Correspondent Author Affiliation**

7. **Funding Source:**
   a. Non-Industry
   b. Industry sponsored
   c. not reported

8. **Study Design:**
   a. RCT
   b. Controlled trial
   c. cohort study
   d. Case control study
   e. Prospective study
   f. Retrospective study

9. **Date of start of study**
   M Year

10. **Date of completion of study**
    M Year

11. **Duration of follow up:**
    Days Months Year

12. **Eligibility criteria were**:
    Explicit
    Not explicit
    Not reported

13. **Inclusion Criteria:**

14. **Exclusion Criteria:**

15. **If Randomized trial:***

a. Method of randomization is described: Yes No
b. If yes describe the method
c. Concealment of allocation is described: Yes No
d. Blinding of patients was done: Yes No
e. Blinding of Health care providers was done: Yes No
f. Blinding of data collectors was done: Yes No
g. Blinding of assessors of outcomes was done: Yes No
h. Blinding of data analysts was done: Yes No
i. Number of patients randomized:
Control Intervention
j. Number of patients not followed:
Control Intervention
k. Number of patients followed but not included:
Control Intervention
l. Number of patients followed but not included in primary analysis:
Control Intervention
m. Intent to treat analysis: Yes N Not Reported

*If a randomized trial found, blinding, follow-up, and intent to treat analysis will be performed separately for each outcome.

16. **If observational study**
a. Cohort studies: The Ottawa/Newcastle quality assessment Score (**See sub-appendix F1 for score**)
b. Case control studies: The Ottawa/Newcastle quality assessment Score (**See sub-appendix F2 for score**)

Baseline Characteristics *(NR=not reported)*

17. Symptomatic
Asymptomatic
Both
Not specified

18. **Number of patients**
a. Total
b. Experimental group
c. Control

19. **Median age**
    a. Experimental group
    b. Control
    c. NR

20. **Age range**
    a. Experimental group
    b. Control
    c. NR

21. **Mean age**
    a. Experimental group
    b. Control
    c. NR

22. **SD of mean age**
    a. Experimental group
    b. Control
    c. NR

23. **Number of female**
    a. Experimental group
    b. Control
    c. NR

24. **% of female**
    a. Experimental group
    b. Control
    c. NR

25. **Comorbid illnesses (number)**
    a. Experimental group
    b. Control
    c. NR

26. **Comorbid illnesses (%)**
    a. Experimental group
    b. Control
    c. NR

27. **ECOG performance status >1 (number)**
    a. Experimental group
    b. Control
    c. NR
    If number not described %
    a. Experimental group
    b. Control
    c. NR

28. **Baseline CEA level (Mean)**
    a. Experimental group
    b. Control
    c. NR

29. **Baseline CEA (SD)**
    a. Experimental group
    b. Control
    c. NR

Primary Tumor

30. **Number of patients with rectal tumor**
    a. Experimental group
    b. Control
    c. NR
    If number not described %
    a. Experimental group
    b. Control
    c. NR

31. **Number patients with colon tumor**
    a. Experimental group
    b. Control
    c. NR
    If number not described %
    a. Experimental group
    b. Control
    c. NR

32. **For colon cancer number in experimental group**
    a. Right colon
    b. left colon
    c. transverse colon
    d. sigmoid colon
    e. NR

33. **If number not described % in experiment group**
    a. Right colon
    b. left colon
    c. transverse colon
    d. sigmoid colon
    e. NR

34. **For colon cancer number in control group**
    a. Right colon
    b. left colon
    c. transverse colon
    d. sigmoid colon
    e. NR

35. **For colon cancer in % experimental group**
    a. Right colon
    b. left colon
    c. transverse colon
    d. sigmoid colon
    e. NR

Disease Burden

36. **Liver disease (number)**
    a. Experimental group
    b. Control
    c. NR

    If number not described %
    a. Experimental group
    b. Control
    c. NR

37. **Liver only disease (number)**
    a. Experimental group
    b. Control
    c. NR

    If number not described %
    a. Experimental group
    b. Control
    c. NR

Extrahepatic disease (number)
    c. Experimental group
    d. Control
    e. NR

If number not described %

a. Experimental group
b. Control
c. NR

38. **Peritoneal disease (number)**
    a. Experimental group
    b. Control
    c. NR

    If number not described %

    a. Experimental group
    b. Control
    c. NR

39. **>25% liver involvement (number)**
    a. Experimental group
    b. Control
    c. NR

    If number not described %

    a. Experimental group
    b. Control
    c. NR

40. **Single site metastases (number)**
    a. Experimental group
    b. Control
    c. NR

    If number not described %

    a. Experimental group
    b. Control
    c. NR

41. **Multiple site metastases (number)**
    a. Experimental group
    b. Control
    c. NR

    If number not described %

    a. Experimental group
    b. Control
    c. NR

42. **Received radiation therapy (number)**
    a. Experimental group
    b. Control
    c. NR

If number not describe%

a. Experimental group
b. Control
c. NR

Systemic Therapy

43. **Received chemotherapy (number)**
    a. Experimental group
    b. Control
    c. NR

    If number not described %

    a. Experimental group
    b. Control
    c. NR

44. **Received 5-FU (number)**
    a. Experimental group
    b. Control
    c. NR

    If number not described %

    a. Experimental group
    b. Control
    c. NR

45. **Received oxaliplatin (number)**
    a. Experimental group
    b. Control
    c. NR

    If number not described %

    a. Experimental group
    b. Control
    c. NR

46. **Received irinotecan (number)**
    a. Experimental group
    b. Control
    c. NR

    If number not described %

    a. Experimental group
    b. Control
    c. NR

47. **Received bevacizumab (number)**
    a. Experimental group
    b. Control
    c. NR

If number not described %
a. Experimental group
b. Control
c. NR

48. **Received anti-EGFR Mabs [cetuximab or panitumumab] (number)**
    a. Experimental group
    b. Control
    c. NR
    If number not described %
    a. Experimental group
    b. Control
    c. NR

49. **Received first-line therapies (number)**
    a. Experimental group
    b. Control
    c. NR
    If number not described %
    a. Experimental group
    b. Control
    c. NR

50. **Received second-line therapies (number) or second-generation therapy**
    a. Experimental group
    b. Control
    c. NR
    If number not described %
    a. Experimental group
    b. Control
    c. NR

51. **Received third-line therapies (number) or third-generation therapy**
    a. Experimental group
    b. Control
    c. NR
    If number not described %
    a. Experimental group
    b. Control
    c. NR

52. **Received second- or third-generation therapy**
    a. Experimental group
    b. Control
    c. NR

If number not described %
a. Experimental group
b. Control
c. NR

Primary Outcome

53. **Median overall survival in months**
    a. Experimental group
    b. Control
    c. NR

54. **Median overall survival range**
    a. Experimental group
    b. Control
    c. NR

55. **One year survival (number)**
    a. Experimental group
    b. Control
    c. NR
    If number not described %
    a. Experimental group
    b. Control
    c. NR

56. **Two year survival (number)**
    a. Experimental group
    b. Control
    c. NR
    If number not described %
    a. Experimental group
    b. Control
    c. NR

57. **Three year survival (number)**
    a. Experimental group
    b. Control
    c. NR
    If number not described %
    a. Experimental group
    b. Control
    c. NR

58. **Five year survival (number)**
    a. Experimental group
    b. Control
    c. NR

If number not described %

a. Experimental group
b. Control
c. NR

Secondary Outcomes (30 days complications, mortality, rate of metastasectomy)

59. **Surgical morbidity in the experimental group (number)**
    NR
    a. Infection
    b. anastomotic leakage
    c. non-infection/non-anastomotic leakage (please specify
    d. Overall number of surgical morbidity

    If number not described %

    a. Infection
    b. anastomotic leakage
    c. others (please specify
    d. Overall % of surgical morbidity

60. **Surgical mortality in the experimental group (number)**
    a. …….
    b. NR

    If number not described %

    a. Overall % of surgical mortality
    b. NR

61. **Primary tumor complications (number in the experimental group)**
    a. Perforation
    b. obstruction
    c. bleeding

62. **Primary tumor complications (% in the experimental group)**
    a. Perforation
    b. obstruction
    c. Bleeding……

63. **Primary tumor complications (number in control group)**
    a. Perforation
    b. obstruction
    c. bleeding

64. **Primary tumor complications (% in control group)**
    a. Perforation
    b. obstruction
    c. bleeding

65. **Rate of metastasectomy %**
    a. Experimental group
    b. Control
    c. NR

66. **Rate of metastasectomy number**
    a. Experimental group
    b. Control
    c. NR

Comparison

67. **Unadjusted risk Difference (Please specify units)**
    a. variance
    b. P value

68. **Adjusted risk Difference (Please specify units)**
    a. variance
    b. P value

69. **Unadjusted risk ratio**

a. hazard ratio	95% CI	P value
b. Odd ratio	95% CI	P value
c. Risk ratio	95% CI	P value
d. Other (specify).	variance	P value

70. **Adjusted risk ratio**

a. hazard ratio	95% CI	P value
b. Odd ratio	95% CI	P value
c. Risk ratio	95% CI	P value
d. Other	(specify variance)	P value

71. **Quality of life score**
    a. Experimental group
    b. Control
    c. NR
    d. Scale

72. **Final outcome**
    a. Favoring experimental arm
    b. Favoring control arm
    c. No difference

APPENDIX E: MANUAL OF DATA ABSTRACTION SHEET

This manual has been written to clarify the electronic data abstraction sheet and to reduce the disagreement between the data extractors. Please follow the steps for the data extraction. **If information is not included in the manuscript, please leave that section blank.** The correspondent authors will be contacted for important missing information.
For each page, please check off your initials and enter the reference number at the top. Each reviewer will complete a form for each study. Consensus will be reached between the two reviewers for differences. Once the differences are resolved by consensus, a final electronic copy will be used for the synthesis of the data.

Study Characteristics

1-7: Please fill the journal name, last name of the first author, location of the study (based on first author affiliation), type of center (single vs. multicenter), correspondent author affiliation, and source of funding.

8: Record the study design if reported and clarify retrospective vs. prospective study (6e and 6f).

8-11: Please record the date of start, date of completion, and the duration of follow-up, if reported.

12-14: Please record if eligibility criteria are explicitly defined, and record the inclusion and exclusion criteria. The study should have only patients with advanced adenocarcinoma of colon and rectum. If the study population is a subgroup of other population, please specified.

15: (13a-13m). Please documents all the bias related to the study if it is a randomized controlled trial. Each outcome will require a separate bias assessment for each outcome specifically for blinding, follow-up and ITT analysis. Please contact the PI (SA).

16: (14a & 14b). Most studies are anticipated to be observational studies. The Ottawa-Newcastle scale will be used to assess the quality of observational study. A study can be awarded a maximum of one point for each numbered item within the Selection and outcome categories. A maximum of two points can be given for Comparability.

Sub appendix F1: Ottawa-Newcastle scale for cohort study. Please score 0-4 points for Selection, 0-2 points for comparability and 0-3 points for outcome with total score of 0-9 of 9.

Sub appendix F2: Ottawa-Newcastle scale for case-control study. Please score 0-4 points for Selection, 0-2 points for comparability and 0-3 points for outcome with total score of 0-9 of 9.

Baseline Characteristics

17: Please record if study population was symptomatic or asymptomatic, if both check both, if it is not clarified please records it.

18-29: Please record total number of study population, median age, age range (mean age and standard deviation [SD]), raw number of female patients and percentage of female patients, percentage of comorbid illness, percentage of patients with ECOG performance status of more than 1 and baseline CEA level (mean and SD). All data must be recorded for both groups (the intervention group and the control).

Primary Tumor

30-35: Items 30-35 are dealt with location of the primary tumor. Please record number and percent of the rectal tumor and colon tumor in both groups. For colon cancer please record the site of the tumor (right, left, transverse, sigmoid) in both groups.

Disease Burden

36-42: Items 36-42 are concerned with the extent of the disease in study population. Please record number and percent of patients with liver disease, liver only disease, disease outside the liver, peritoneal disease, >25% liver involvement, single site metastases, and multiple site metastases in the intervention and control groups.

43: Please record if number and percent of patients in both groups received palliative radiation therapy.

Systemic Therapy

44-53: Items 44-53 are related to types of chemotherapy and biologics, and number of lines of therapy in the intervention and control groups. Please record number or percent of patients in both groups received chemotherapy, 5-FU, oxaliplatin, irinotecan, bevacizumab, anti-EGFR-mabs [cetuximab, panitumumab], first-line therapy, second-line therapy, third-line therapy, and second- or third-generation therapy.

Primary Outcome (Survival)

54-59: Items 54-59 deal with survival of patients in both groups.
54-55: Please record median overall survival in months and range of survival.
56-59: Please record number or percent of patients with 1-year survival, 2-year survival, 3-year survival, and 5-year survival in both groups.

Secondary outcomes (30 days complications, mortality, rate of metastasectomy)

60-67: Items 60-67 are concerned with the secondary outcomes including post-operative mortality, morbidity, and rate of metastasectomy.
60. Please record surgical morbidity number and percent for the experimental group described in a study (Ideally 30 days post-op). Infection is defined as all documented surgical wound and other infection related to the surgery and reported. For 58c"non-infection/non-anastomotic leakage" please specify the total number.

61. Please record surgical mortality (number and percent) in the experimental group.

62-65: Please record primary tumor complications (number and percent) in the experimental and control group. A primary tumor complication is defined as proportion of bleeding, obstruction, and perforation in the control group.

66-67: Please record number and percent of metastasectomy in both groups.

Comparison

68-69: Please record unadjusted and adjusted risk difference between the two groups, with reported variance (95% CI), and P-value if it is reported.

70: Please record unadjusted risk ratio (e.g. hazard ratio) between the two groups, with reported variance (95% CI), and P-value if it is reported.

71: Please record adjusted risk ratio between the two groups, with reported variance (95% CI), and P-value if it is reported.

72: Please record quality of life score and scale used in the two groups.

74: Please record the primary outcome reported in a study comparing surgery vs. nonsurgical group, record if there was no difference in mortality, or if the survival of one the groups was superior.

APPENDIX F1- NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE: COHORT STUDIES (PRIMARY OUTCOME: MORTALITY)

For cohort study these items are as follow (**Appendix 3a**). Selection: (1) true representativeness of the exposed cohort in the community, (2) non exposed cohort drawn from the same community, (3) ascertainment of exposure, and (4) demonstration that outcome of interest was not present at start of study. Comparability of cohorts: (5) control for symptoms and (6) control for systemic therapy. Outcome: (7) assessment of outcome, (8) follow–up was long enough for outcomes to occur and (9) adequacy of follow-up of cohorts.

A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection (0-4)
Comparability (0-2)
Outcome (0-3)

Total: 0-9

Selection

1. Representativeness of the exposed cohort
   a. True representative of the patients with advanced colorectal cancer in the community*
   b. Somewhat representative of the patients with advanced colorectal cancer in the community*
   c. Selected group
   d. No description of the derivation of the cohort

2. Selection of the non-exposed cohort
   a. Drawn from the same community as the exposed cohort*
   b. Drawn from a different source
   c. No description of the derivation of the non-exposed cohort

3. Ascertainment of exposure
   a. Secure record*
   b. Structured interview*
   c. Written self-report
   d. no description

4. Demonstration that outcome of interest was not present at start of study
   a. Yes*
   b. No

Comparability

1. Comparability of cohorts on the basis of the design or analysis
   a. Study controls for symptoms*
   b. Study controls for systemic therapy*

Outcome

1. Assessment of outcome
   a. Independent blind assessment*
   b. Record linkage*
   c. Self-report
   d. No description

2. Was follow-up long enough for outcomes to occur
   a. Yes (select an adequate follow up period for outcome of interest)*
   b. No

3. Adequacy of follow-up of cohorts
   a. Complete follow-up - all subjects accounted for*
   b. Subjects lost to follow-up unlikely to introduce bias - small number lost <5% or description provided of those lost)*
   c. Follow-up rate <5% and or no description of those lost
   d. No statement

……../4, ……../2,……../3= ……../9
Total score

APPENDIX F2 - NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE: CASE-CONTROL STUDIES

For case control study these items are as follow. Selection: (1) Case definition, (2) representativeness of the cases, (3) selection of controls, and (4) definition of controls. Comparability of cohorts: (5) control for symptoms and (6) control for systemic therapy. Exposure: (7) assessment of exposure, (8) same method of ascertainment for cases & controls, and (9) non-response rate

A study can be awarded a maximum of one star for each numbered item within the Selection and outcome categories. A maximum of two stars can be given for Comparability

Selection (0-4)
Comparability (0-2)
Outcome (0-3)

Total: 0-9

Selection

1) Is the case definition adequate?
   a) Yes, with independent validation*
   b) Yes, e.g. record linkage or based on self-reports
   c) No description

2) Representativeness of the cases
   a) Consecutive or obviously representative series of cases*
   b) Potential for selection biases or not stated

3) Selection of Controls
   a) Community controls*
   b) Hospital controls c) no description

4) Definition of Controls
   a) No history of disease (endpoint)*
   b) No description of source

Comparability

1) Comparability of case and controls on the basis of the design or analysis
   a) Study controls for symptoms*
   b) Study controls for systemic therapy*

Exposure

1) Ascertainment of exposure
   a) Secure record*
   b) Structured interview were blind to case/control status*
   c) Written self report or medical record only
   d) No description

2) Same method of ascertainment for cases & controls
   a) Yes*
   b) No

3) Non-Response rate
   a) Same rate for both groups*
   b) Non respondents described
   c) Rate different and no designation

……..…../4, ……./2,……../3= ……../9
Total score

APPENDIX F3- PROTOCOL OF DATA EXTRACTION

Two reviewers will select trials and extract the data using pre-determined forms independently. Data will be compared for differences. If there is a difference, it will be resolved by consensus

- study design
- population characteristics
- Intervention
- outcomes measures
- results

APPENDIX G1 (1992-2005) - COLO-RECTAL CANCER ABSTRACTION SHEET

Date of birth (D/M/Y): _____ **Gender:** M F

Major Comorbid illness: NA None CAD DM CRI COPD Others - _____

Secondary cancer: Y N **ECOG PS**: 0 1 2 3 4 NA

Current Smoker: Y N NA **EX Smoker:** Y N NA

Baseline: Na _____ Creatinine _____ BUN _____ Albumin _____ Bilirubin _____ CEA _____

Alk P _____ AST _____ ALT _____ LDH _____ WBC _____ Hb _____ Plt _____

Previous diagnosis of early stage colon cancer: Y N (if yes exclude)

Date of diagnosis of advanced colorectal cancer (D/M/Y) _____

Colon (RT T Lt Sig) Rectal Rectosigmoid Appendix NOS Overlap **Code** _____

T _____ **N**_____/_____ **Grade** _____

Obstruction: Y N **Perforation:** Y N **Heavy Bleeding:** Y N

Mucinous: Y N

Surgery for primary tumor: Y N **Surgery for mets**: Y N

Sites of Mets: Liver Extra hepatic: N Y (lung peritoneum Bone CNS Others_____)

Received chemotherapy: Y N

Date of start of chemotherapy (D/M/Y) _____

Received 2nd line therapy: Y N

Received RT: Y N **Irinotecan/oxaliplatin**: Y N

Date of last contact on which the status of disease was evaluated (D/M/Y) _____

Alive **Deceased** **Date of death (D/M/Y)** _____

APPENDIX G2 (2006-10) COLO-RECTAL CANCER COHORT

Medical Record Number: _____

Date of Birth (D/M/Y): _____ **Gender:** M F **Postal Code:** _____

Status at Time of Diagnosis: Single Married Widow Common-Law Unknown

Children: Y N

Major Co morbid Illness: NA None CAD DM CRI COPD Others_____

Secondary Cancer: Y N **ECOG PS**: 0 1 2 3 4 NA NK

Current Smoker: Y N NA **EX Smoker:** Y N NA

Baseline:
Na_____Creatinine_____BUN_____Albumin_____Bilirubin_____CEA_____

Alk
P_____AST_____ALT_____LDH_____WBC_____Hb_____Plt_____

Previous Diagnosis of Early Stage Colon Cancer: Y N ***(IF YES EXCLUDE)***

Date of Diagnosis of Advanced Colorectal Cancer (D/M/Y):
_____

Colon: (RT T Lt Sig) Rectal Rectosig Appendix NOS Overlap

Code: _____ **T**_____ **N**_____/_____ **Grade** _____

Obstruction: Y N **Perforation:** Y N **Heavy Bleeding:** Y N

Mucinous: Y N **Moderate to Severe Pain:** Y N

Surgery for Primary Tumor: Y N **Date of Surgery of Primary Tumor (D/M/Y/):**_____

Non-Surgical Procedure: Y N **If Yes**: Stent Ostomy Other: _____

Surgery for Mets: Y N **Date of Start of Surgery of Mets (D/M/Y/)**:_____

Sites of Mets: Liver Extra hepatic: N Y (lung peritoneum Bone CNS Others_____)

Received Chemotherapy: Y N

Date of Start of Chemo (D/M/Y): _____ Date of End of Chemo (D/M/Y): _____

Received 2nd Line Therapy: Y N

Received 3rd Line Therapy: Y N

Received Irinotecan: Y N

Received Oxaliplatin: Y N

Received Bevacizumab (Avastin): Y N

Received Cetuximab or Panitumumab: Y N

Received RT: Y N **Radical /Palliative**

Radiotherapy Start Date (D/M/Y): _____Radiotherapy End Date (D/M/Y): _____

Date of Last Contact on Which the Status of Disease was E valuated (D/M/Y): _____

Alive Deceased

Date of Death (D/M/Y): _____

Cause of Death (D/M/Y): _____

APPENDIX H: DATA COLLECTION MANUAL (COHORT STUDY)

Medical Record Number	clinic chart number of the patient
Date of Birth (D/M/Y)	date of birth of patient
Gender	M=Male F=Female
Postal Code	postal code at time of diagnosis
Status at Time of Diagnosis	single, married, widow, common-law, unknown at time of diagnosis
Children	any children (Yes/No) do not need to be biological children; need to know if patient has children around for possible support
Major Co Morbid Illness	NA= Not Available None= None CAD= coronary artery disease DM=diabetes mellitus CRI= chronic renal insufficiency COPD- chronic obstructive pulmonary disease Other=anything that does not appear above (include angina, ischemic, hypertension, MI here) (PI will look through and determine if comorbid or not)
Secondary Cancer	Yes No Indicates if a patient has had an additional cancer other than the colorectal cancer at any time (before or after diagnosis of Colorectal); exclude skins (Basal cell & Squamous) but include melanomas; exclude benign cases
ECOG PS	Performance status of patient at first clinic visit. (Use performance scale sheet); if unable to figure it out use NA (not available) as per PI, if not stated, try to determine using **1** (as ECOG 0 or 1) and **2** (as ECOG 2 or higher)
Current Smoker	Yes No Not Available or NK If patient said to be a smoker but not clear whether they still smoke = smoker; if patient does snuff/chewing tobacco: do not include = NO
EX Smoker	Yes No NA (not indicated in chart) Yes = if patient does not currently smoke but did at one time in their life

Baseline Labs Use lab values from around first clinic visit – Na, Creatinine, BUN (Urea), Albumin, Bilirubin, CEA, AlkP (AlkPhos), AST (SGOT), ALT(SGPT), LDH ,WBC, Hb, Plt

Previous Diagnosis of Early Yes = Exclude No

Stage Colon Cancer previous diagnosis of early stage colon = exclude

Date of Diagnosis of histological proven date of diagnosis of colorectal or metastasis from

Advanced Colorectal Cancer colorectal biopsy date can be used (must have tissues DX to be included)

(D/M/Y)

Colon
RT= right (C18.0 cecum), ascending (C18.2)
T= transverse (C18.4), hepatic (C18.3), splenic (C18.5)
Lt= left, descending (C18.6)
Sig= sigmoid (C18.7)
Rectal (C20.9)
Rectosigmoid (C19.9)
Appendix (C18.1) included (email June 15, 2007)
NOS (Not Otherwise Specified) (NK) (email Dec 6/06) (C18.9)
Overlapping Lesion of Colon (C18.8)

T Primary Tumor
USE AJCC 6th edition to Stage "T" (TX, TO, Tis, T1, T2, T3, T4)

N number of nodes positive and number of nodes examined (3/11= three nodes positive out of the eleven nodes examined) - if not indicated as to how many involved/examined. Use "?/#"

Grade
1= Well
2= Moderate
3= Poor
4= Undifferentiated
9=Grade Not Determined

Obstruction Yes No **********

Obstruction is defined as either acute obstruction on presentation or obstruction seen on endoscopy or obstruction evident on pathologic specimen
Can be clinical or pathological
Can be complete or partial

Perforation Yes No
Defined as abdominal crisis due to escape of contents of perforated viscous into peritoneal cavity
Perforation= T4
Some T4's are included and some excluded from study.
(See additional "T4" sheet for guide)

Heavy Bleeding Yes No
Patient anemic = No
On presentation and/or surgery
Surgery in advanced patients is usually not done unless there is bleeding (Drop in hemoglobin <20 g/l)
It is up to treating surgeon if he felt bleeding was significant and required palliative surgery than consider heavy bleeding. It does not mean bleeding during surgery. (Email July 2, 2008)

Mucinous Yes No
If stated as 50% or more in the pathological description: it will be "yes". It will be "Yes" if stated in final diagnosis of path

Moderate to Severe Pain unpleasant sensation the can range from mild, localized discomfort to agony around the time of diagnosis

Surgery for Primary Tumor Yes No
Did patient have surgery for the primary tumor
It is the resection of tumor not biopsy or formation of defunctioning colostomy to bypass obstruction (email Feb27/07)
Must be a resection to be surgery for primary tumor.

Date of Surgery of Primary initial date of surgery of the primary tumor: D/M/Y

Tumor

Non-Surgical Procedure did patient have a stent, ostomy or something else

Surgery for Metastases (liver, lung, etc) Yes No
did patient have surgery for metastasis of the liver etc. (does not need to be complete resection)

Dates of Surgery of Mets initial date of start of surgery of mets: D/M/Y

Sites of Mets: Liver (circle if yes)
Extrahepatic: circle Yes or No (lung, peritoneum, Bone, CNS, Others)

	Only at time of diagnosis (based on most recent imaging study after diagnosis (email Dec15/06) If at time of surgery they had lesions which subsequently turn out to be mets; include. However, for patients with normal presurgical imaging studies and no suspicious lesion during surgery we will still require 6 weeks eligibility criteria. (Email April 12, 2007)
Received Chemotherapy	Yes No Any time since diagnosis of advanced cancer (make sure it's not a T4 are not eligible if there is direct extension)
Date of Start of Chemo (D/M/Y)	date patient received cycle 1 of chemo no matter what the regimen was (5-FU/ Leucovorin, Tomudex, CPT 11 etc.) This is for the very **FIRST** chemo regimen patient received
Date of End of Chemo	End date of chemo D/M/Y
Received 2nd Line Therapy	Yes No If patient received any more than one type of chemo regimens ex. 5U/Leucovorin, then CPT11: CPT 11 would be 2nd line therapy
Received 3rd Line Therapy	Yes No If patient received any more than two types of chemo regimens ex. 5-FU/Leucovorin, then CPT11, then Xeloda: Xeloda would be 3rd line therapy
Received Irinotecan (CPT-11, Campstosar)	Yes No clinical trials are also included
Received Oxaliplatin (Eloxatin)	Yes No clinical trials are also included
Received Bevacizumab (Avastin)	Yes No clinical trials are also included
Received Cetuximab (Erbitux) or Panitumumab (Vectibix)	Yes No clinical trials are also included -this is if patient had *either one of them or both*
Received RT	Yes No (Radical, palliative or adjuvant) (Phone call Dec 22/06) No specific details needed

Radical/Palliative	the kind of radiotherapy patient was receiving: Radical or Palliative
Radiotherapy Start Date (D/M/Y)'	date that patient started Radiotherapy
Radiotherapy End Date (D/M/Y)	date that patient ended Radiotherapy
Date of Last Contact on Which the Status of Disease was Evaluated if Patient was alive (D/M/Y)	can use clinic note, family physician note, FBM letter use date of death if patient expired
Alive	patient is alive at the time of data extraction
Deceased	patient is deceased at the time of data extraction
Date of Death (D/M/Y)	date of death If exact date is not known use 01/01/9999
Cause of Death	**T**he reason the person died Use the death information in the registry

APPENDIX I:

TABLE I1 CONVERSION OF KARNOFSKY PERFORMANCE STATUS SCALE INTO ECOG PERFORMANCE STATUS

WHO/ECOG Performance Status		Karnofsky Performance Status	
0	Able to carry out all normal activity without restriction	100	Normal no complaints; no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self; unable to carry on normal activity or to do active work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his personal needs.
		50	Requires considerable assistance and frequent medical care.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled; requires special care and assistance.
		30	Severely disabled; hospital admission is indicated although death not imminent.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	20	Very sick; hospital admission necessary; active supportive treatment necessary.
		10	Moribund; fatal processes progressing rapidly.
5	Dead	0	Dead

APPENDIX J SAMPLE SIZE CALCULATION

Power=90
Alpha error 0.05 with two tailed
Ratio 1:2 (q0:q1)
Hazard reduction=0.80 (20% reduction in mortality)
Baseline event rate =0.077
Baseline censor=0.05
Median survival of control=9 months
Follow up period=60 months

APPENDIX K: RELATIONSHIP BETWEEN AREA LEVEL VARIABLES AND SURVIVAL

Results

The postal code information was obtained for 569 patients who were diagnosed with synchronous stage IV CRC. By using the Postal Code Conversion File (PCCF), the postal code information was linked to the Census subdivision. The following area level variables were examined with respect to their correlation with overall survival. Average household income, average family income, age dependency ratio, unemployment rate, labor force participation, proportion of aboriginal population, high school certificate rates, single parent, foreign born, minority and socio-economic Factor Index 2 (SAFEI2).The mean and median values were obtained (**Table A11.1**).

Table K1: Mean and median values of area level variables.

Variables	Mean SD ±	Median (IQR)
Average Family Income	70968 ± 11968 CAD	70056 (64096-79852)
Average House Income	57804 ±10443 CAD	56795 (52207-64254)
Unemployment Rates	0.058 ±5.37	0.05 (4-6)
Labor Force Participation	0.81 ±0.13	0.82 (0.80-0.85)
Aboriginal Proportion	0.11 ±0.14	0.09 (0.03-0.10)
Age Dependency Ratio	0.57 ±0.15	0.57 (0.45-0.67)
Minority Proportion	0.037 ±0.036	0.027 (0.004-0.07)
No High School Graduation	0.40 ±0.36	0.37 (0.26-0.50)
Single Parent Household	0.17 ±0.06	0.18 (0.13-0.19)
Foreign Born	0.05 ±0.03	0.05 (0.03-0.08)

IQR: inter quartile range

Using a cut-off of median values, all variables were categorized into two categories. Furthermore, using quartile values each variable was categorized into 4 groups (**Table A11.2**).

Table K2: Different quartiles of area-level variables.

Area Level Variables	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Household income	52207 CAD	52208-56759 CAD	56760-64254 CAD	64255 and above CAD
Family income	64096 CAD	64097-70056 CAD	70057-79852 CAD	79853 and above CAD
Age Dependency ratio	0.45	0.46-0.57	0.58-0.67	0.68 and above
Unemployment rateŦ	4.0	4.1-5.0	5.1-6.0	6.1 and above
Aboriginals	0.031	0.032-0.093	0.094-0.099	0.10 and above
Single Parent*	0.1321	0.1322-0.1800	0.1801-0.1926	0.1927 and above
High schools certificate§	0.257	0.258-0.367	0.368-0.500	0.501 and above
SAFEI2ψ	-0.2401100	-0.2401099 to -0.0586400	-0.0586399 to 0.2218800	0.2218801 and above

*Proportion of single-parent families. ŦUnemployment rate for labor force population aged 15 years and older. §Proportion of population 15 years and older without high school graduation.ψSocio-economic Factor Index 2

Kaplan-Meier Survival analysis was performed to compare survival of each category and quartile. The log-rank tests were performed and survival curves of different categories and quartiles were compared. No significant differences were noted in the survival of individuals from low income, high unemployment rate, and lower high school certification areas versus individuals from high income, low unemployment rate, and higher high school certification areas, respectively (**Table A11.3**). Furthermore, no significant differences were noted in the survival of individuals from different SAFEI2 quartiles (**Figure A11.1**).

Table K3: Survival of individuals from various geographical regions based on several socio-economic variables.

Variable	Number 569	Mean 95% CI	Median 95% CI	P values
SAFEI2				0.29
-0.2401100 or below	145	15.5 (12.6-18.4)	11 (6.1-15.9)	
-0.2401099 to -0.0586400	145	19.0 (15.1-22.8)	9 (4.9-13.1)	
-0.0586399 to 0.2218800	158	19.7 (16.5-22.9)	12 (7.4-16.6)	
0.2218801 and above	119	19.6 (15.3-23.8)	11 (7.4-14.6)	
Unemployment Rate				0.80
<0.05	296	18.1 (15.6-20.6)	9 (6.2-11.8)	
≥0.05	273	19.1 (16.5-21.7)	12 (8.8-15.20	
Single Parent				0.65
<0.18	312	18.2 (15.7-20.8)	11 (8.4-13.6)	
≥0.18	257	18.7 (16-21.3)	11 (7.4-14.6)	
Labor Force Participation				0.93
≥0.81	265	18.2 (15.6-20.1)	11 (8.3-13.7)	
<0.81	304	19.1 (16.5-21.7)	11 (7.9-14.1)	
No High School Graduation				0.37
<0.37	276	17.9 (15.3-20.4)	10 (7.3-12.7)	
≥0.37	293	19.0 (16.5-21.5)	12 (8.8-15.2)	
Foreign Born				0.52
≥0.05	247	18.8 (16.1-21.6)	11 (7.6-14.4)	
<0.05	322	18.2 (15.8-20.7)	11 (8.2-13.8)	
Aboriginal				0.58
≥0.09	298	19.4 (16.6-22.2)	10 (6.8-13.2)	
<0.09	271	17.5 (15.2-19.9)	11 (8.0-14.0)	
Average Household income				0.24

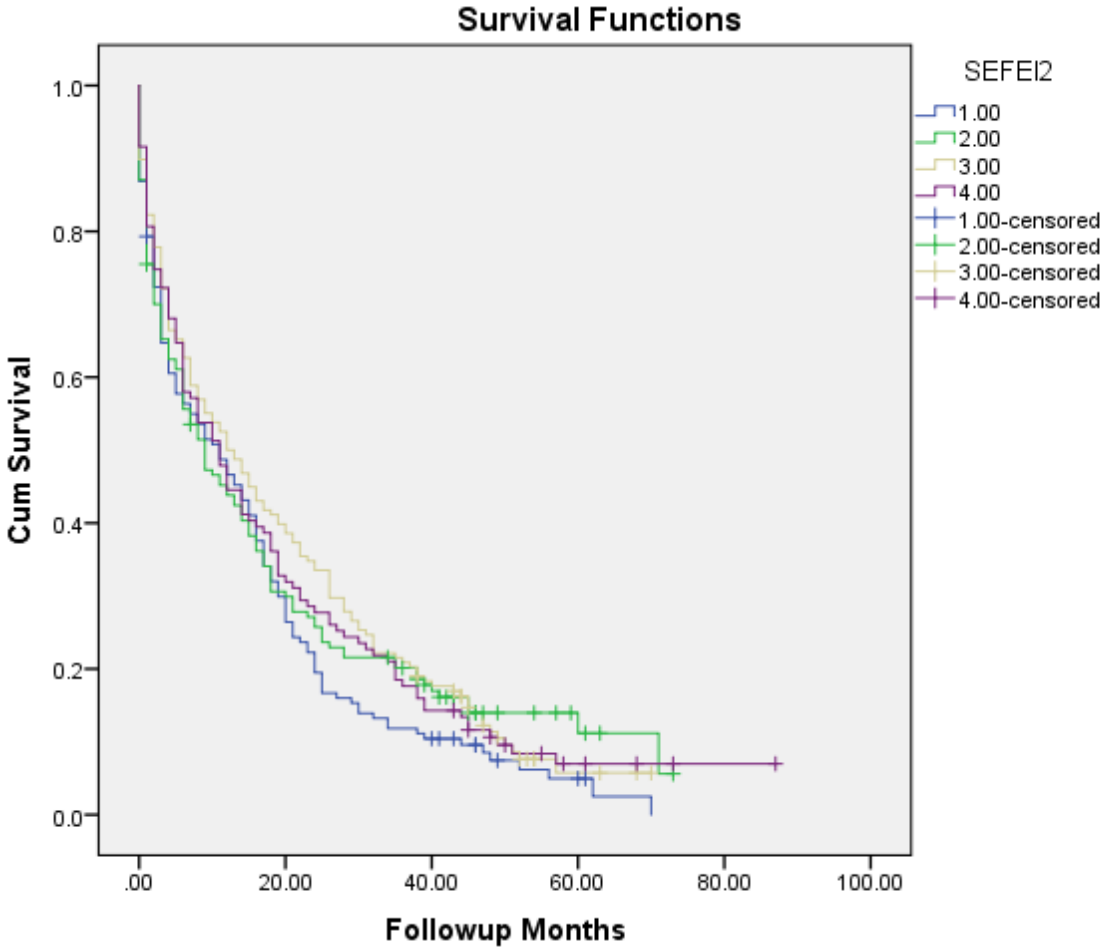
<56795 CAD	285	17.5 (15.1-20.0)	11 (7.7-14.3)	
≥56795 CAD	284	19.2 (16.6-21.8)	11 (8.0-14.0)	
Minority				0.16
<0.037	277	19.4 (16.8-22.0)	11 (8.1-13.9)	
≥0.037	292	17.4 (15.0-19.8)	11 (7.7-14.3)	
Age Dependency Ratio				0.91
≥0.57	283	18.1 (15.7-20.4)	11 (8.0-14.0)	
<0.57	286	19.0 (16.2-21.8)	11 (8.0-14.0)	
Family income low				0.80
<70056	285	18.9 (16.2-21.6)	12 (8.8-15.2)	
≥70056	284	18.4 (15.9-20.9)	10 (7.4-12.6)	

Cox models with shared frailty were fitted. The individual clinicopathological variables that demonstrated correlation with survival in a multivariate Cox Proportional Hazard model were used in the model: chemotherapy, surgical resection of primary tumor, metastasectomy, second-line therapy, third-line therapy, elevated alkaline phosphatase, grade 3 tumor, leukocytosis, stage IVb disease, and ECOG performance status of >1. For income, unemployment rates, proportion of foreign born and SAFEI2, the STATA software could not calculate numerical derivatives. For the other variables, relationships were not significant (**Table A11.4**).

Table K4: Result of Cox models with shared frailty for various area level variables.

Variables	Theta		P
Average Family Income	could not calculate numerical derivatives		
Average Household Income	could not calculate numerical derivatives		
SAFEI2	could not calculate numerical derivatives		
Unemployment Rate	could not calculate numerical derivatives		
Aboriginal population	3.51e-18	4.74e-14	0.5
Labor Force Participation	2.41e-18	5.57e-14	0.5
Age Dependency ratio	4.47e-29	2.54e-24	0.5
Foreign Born	could not calculate numerical derivatives		
Minority	3.51e-18	6.18e-14	0.5
Single Parent	3.51e-18	6.18e-14	0.5

Figure K1: Survival of patients with different SAFEI2 scores.



APPENDIX L: CERTIFICATE OF ETHICS APPROVAL

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Re-Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Shahid Ahmed	Medical Oncology	06-44

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
Saskatoon Cancer Centre
20 Campus Drive
Saskatoon SK S7N 4H4

SUB-INVESTIGATOR(S)
Amer Sami, Imran Ahmad, Sunil Yadav, Kamal Haider, R K Shahid, Riaz Alvi

FUNDER(S)
UNFUNDED

TITLE
Prognostic Role of Surgical Resection of Primary Tumor in Metastatic Colorectal Cancer

RE-APPROVED ON	EXPIRY DATE
25-Sep-2015	24-Sep-2016

Delegated Review ☒ Full Board Meeting ☐

CERTIFICATION
The study is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This re-approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://www.usask.ca/research/ethics_review/.

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In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. This re-approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board has been approved by the Minister of Health, Province of Saskatchewan, to serve as a Research Ethics Board (REB) for research projects involving human subjects under section 29 of The Health Information Protection Act (HIPA).

Lori Ebbesen

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Lori Ebbesen, Ed.D.
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Ahmed S, Leis A, Kanthan S, Fields A, Reeder B, Iqbal N, Haider K, Le D, Pahwa P. Surgical management of the primary tumor in stage IV colorectal cancer: a confirmatory retrospective cohort study. Journal of Cancer (In press).
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APPENDIX N – NEWCASTLE SCORE FOR OBSERVATIONAL STUDIES ANALYZED IN META-ANALYSIS

Aslam et al

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Selected group (Single institutional)	0
2	Selection of the non-exposed cohort	
	Source not known (non-community)	0
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	1
6	Study controls for systemic therapy	0
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	Yes (>5 years of study duration)	1
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	5

Benoist et al

Items	Selection	Score
1	Is the case definition adequate?	
	Yes, eg record linkage or based on self	0
2	Representativeness of the cases	
	Consecutive or obviously representative series of cases	1
3	Selection of Controls	
	Hospital controls	0
4	Definition of Controls	
	No history of disease (endpoint)	1
	Comparability	
5	Study controls for symptoms	1
6	Study controls for systemic therapy	1
	Exposure	
7	Ascertainment of exposure	
	Secure record	1
8	Same method of ascertainment for cases & controls	
	Yes	1
9	Non-Response rate	
	rate different and no designation	0
	Total Score ……/9	6

Chan et al

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Somewhat representative of the patients with advanced colorectal cancer in the community	1
2	Selection of the non-exposed cohort	
	Drawn from the same community as the exposed cohort	1
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	0
6	Study controls for systemic therapy	0
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	No (<5 years of study duration)	0
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	5

Evan et al

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Selected group (Single institutional)	0
2	Selection of the non-exposed cohort	
	Source not known (non-community)	0
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	0
6	Study controls for systemic therapy	0
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	Yes (>5 years of study duration)	1
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	4

Galizia et al

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Selected group (Single institutional)	0
2	Selection of the non-exposed cohort	
	Source not known could be from a different source (non-community)	0
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	1
6	Study controls for systemic therapy	1
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	Yes (>5 years of study duration)	1
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	6

Karoui et al

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Selected group	0
2	Selection of the non-exposed cohort	
	Source not known may be from a different source (non-community)	0
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	0
6	Study controls for systemic therapy	1
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	Yes (>5 years of study duration)	1
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	5

Konylian et al

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Selected group (Single institutional)	0
2	Selection of the non-exposed cohort	
	Source not known may be from a different source (non-community)	0
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	0
6	Study controls for systemic therapy	1
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	Yes (>5 years of study duration)	1
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	5

Michel et al

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Selected group (Single institutional)	0
2	Selection of the non-exposed cohort	
	Source not known, may be from a different source (non-community)	0
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	1
6	Study controls for systemic therapy	0
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	No (<5 years of study duration)	0
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	4

Ruo et al

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Selected group (Single institutional)	0
2	Selection of the non-exposed cohort	
	Source not known (non-community)	0
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	1
6	Study controls for systemic therapy	0
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	No (<5 years of study duration)	0
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	4

Scoggins et al

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Selected group (Single institutional)	0
2	Selection of the non-exposed cohort	
	Source not known (non-community)	0
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	0
6	Study controls for systemic therapy	0
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	Yes (>5 years of study duration)	1
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	4

Seo et al

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Selected group (Single institutional)	0
2	Selection of the non-exposed cohort	
	Source not known, may be from a different source (non-community)	0
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	1
6	Study controls for systemic therapy	1
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	Yes (>5 years of study duration)	1
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	6

Tebutt et al

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Selected group (Single institutional)	0
2	Selection of the non-exposed cohort	
	Source not known (non-community)	0
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	1
6	Study controls for systemic therapy	0
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	Yes (>5 years of study duration)	1
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	5

Temple et al

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Somewhat representative of the patients with advanced colorectal cancer in the community	1
2	Selection of the non-exposed cohort	
	Drawn from the same community as the exposed cohort	1
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	0
6	Study controls for systemic therapy	0
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	Yes (>5 years of study duration)	1
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	6

Venderbosch et al (CAIRO)

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Somewhat representative of the patients with advanced colorectal cancer in the Community (a subgroup of randomized patients across Netherland)	1
2	Selection of the non-exposed cohort	
	Drawn from the same community as the exposed cohort (a subgroup of Randomized patients across Netherland)	1
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	0
6	Study controls for systemic therapy	1
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	Yes (>5 years of study duration)	0
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	6

Venderbosch et al (CAIRO II)

Items	Selection	Score
1	Representativeness of the exposed cohort	
	Somewhat representative of the patients with advanced colorectal cancer in the Community (a subgroup of randomized patients across Netherland)	1
2	Selection of the non-exposed cohort	
	Drawn from the same community as the exposed cohort (a subgroup of Randomized patients across Netherland)	1
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	0
6	Study controls for systemic therapy	1
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	Yes (>5 years of study duration)	0
9	Adequacy of follow up of cohorts	
	No statement	0
	Total Score ……/9	6

APPENDIX O – NEWCASTLE SCORE FOR THE AUTHOR'S COHORT STUDIES

Ahmed et al (1992-2005 Cohort)

Items	Selection	Score
1	Representativeness of the exposed cohort	
	True representative of the patients with advanced colorectal cancer in the community	1
2	Selection of the non-exposed cohort	
	Drawn from the same community as the exposed cohort	1
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	1
6	Study controls for systemic therapy	1
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	Yes (>5 years of study duration)	1
9	Adequacy of follow up of cohorts	
	Complete follow up - all subjects accounted for	1
	Total Score ……/9	9

Ahmed et al (2006-2010 Cohort)

Items	Selection	Score
1	Representativeness of the exposed cohort	
	True representative of the patients with advanced colorectal cancer in the community	1
2	Selection of the non-exposed cohort	
	Drawn from the same community as the exposed cohort	1
3	Ascertainment of exposure	
	Secure record	1
4	Demonstration that outcome of interest was not present at start of	
	Yes	1
	Comparability	
5	Study controls for symptoms	1
6	Study controls for systemic therapy	1
	Outcome	
7	Assessment of outcome	
	Record linkage	1
8	Was follow-up long enough for outcomes to occur	
	Yes (>5 years of study duration)	1
9	Adequacy of follow up of cohorts	
	Complete follow up - all subjects accounted for	1
	Total Score ……/9	9